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AN EVALUATION OF CHLOROTHIAZIDE IN THE TREATMENT OF EDEMA IN PREGNANT WOMEN*

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DIURETIC agents have played an important part in the empiric treatment of pregnancy toxemia. This paper presents an evaluation of a new diuretic sulfonamide, chlorothiazide,† (6-chloro-7-sulfamyl-1, 2, 4 benzothiadiazine-1, 1-dioxide), which was "tailor made" to inhibit carbonic anhydrase. This does not appear to be the mechanism of its desirable action, however, for it stimulates almost equimolar excretions of sodium and chloride without the bicarbonate loss seen as an effect of acetazoleamide. Potassium excretion is also increased by the drug, especially when the natriuretic effect is not marked.[1]

Evaluation of diuretic drugs in pregnant women with edema poses some peculiar difficulties. When such women are hospitalized and kept on a low-sodium intake, they typically lose weight, water, and sodium for a week to 10 days and may become edema free with no other treatment (unless they have severe pre-eclampsia). While this is often true in nonpregnant edematous patients as well, the effect is more marked in pregnant women. In pregnancy the venous pressure (and therefore capillary pressure) is considerably increased in the legs, thus favoring filtration of fluid out of the vascular system, especially when the patient is up and about. In the pleasingly proportioned woman the

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†Marketed as Diuril by Merck Sharp & Dohme, West Point, Pa.

legs make up about 38 per cent of the body weight[2] and therefore constitute a large reservoir for interstitial (edema) fluid. With bed rest the venous pressure in the legs decreases, thus favoring reabsorption of the interstitial fluid, and in normal pregnancy the volume of night urine may exceed that of the day.[3] Bed rest is one of the best diuretics in pregnant edematous women. The clinician's impression as to the efficacy of a diuretic drug is often confused by the fact that his patient is almost simultaneously hospitalized, put on a low sodium intake, and started on the drug; the prompt weight loss is then attributed to the drug.

Methods

In the balance studies, done in 4 control patients, each item of food given to the patients was weighed and an exact duplicate saved for analysis. All food rejected by a patient was saved and analyzed separately. The duplicate of the day's diet was homogenized in a Waring blendor, with tap water to match the amount consumed by the patient; if more water was needed to make the slurry, the extra amount was made up by distilled water. The homogenate was weighed (usually 2,500-3,000 Gm.) and duplicate aliquots (3 to 5 Gm.) were accurately weighed for analysis. These were wet-ashed[4] and the digests then diluted to suitable volumes for flame photometric readings (100 ml. for sodium and this further diluted 1:5 for potassium). Rejected portions of the diet and fecal output of the patients were treated in the same way. All urine was collected, in 24 hour periods, and the completeness of collection checked by measurements of creatinine excretion. Sodium and potassium analyses were done with a Perkin-Elmer 52C flame photometer, with an internal lithium standard. Blank analyses showed that the acid digestion mixture was free of sodium and potassium. The acidity of the final solutions analyzed did not affect the results, as shown by recovery experiments.

In the studies of chlorothiazide effects, the patients used had been in the hospital, in bed most of the time, and on a low-sodium diet for at least 4 days (average 6 days) before the drug was started. On the day before, the plasma volume was measured with T-1824 and the 4 hour sodium space and 24 hour exchangeable sodium with 30 μc. of sodium^{24}. Measurements of the volume of sucrose distribution (extracellular fluid volume ?) were not satisfactory because equilibrium could not be established. The 24 hour urine collected in connection with measurement of the exchangeable sodium was analyzed for sodium, potassium, chloride,[4] protein,[4] and creatinine[5] excretions, as were the 24 hour urine specimens collected daily throughout the whole period of observation. Balance studies were not done, but from analyses of our low-sodium diet made over 54 almost consecutive days it was estimated that the average sodium intake was 30 mEq. and the average potassium intake 90 mEq. per day. (The sodium varied only slightly from day to day but the potassium ranged from 57 to 122 mEq.)

The patients were given 1 Gm. of chlorothiazide per day, half in the morning and half in the early evening, for 6 consecutive days. Remeasurements were made on the seventh day of the plasma volume, 4 hour sodium space, and 24 hour exchangeable sodium. After 3 days off the chlorothiazide, 3 patients were put back on and the observations continued throughout. Two patients were excluded from the analyses because creatinine measurements indicated erratic collections of urine. Others went into labor or left the hospital before the full cycle of observations could be made.

Results

The effect of bed rest and sodium restriction alone upon the net loss of sodium is shown for 4 patients in Fig. 1. Two of the patients, both with pre-eclampsia, went into labor shortly after being started on the balance study. The other 2, both of whom had edema but could not be called pre-eclamptic, were in negative sodium balance for 10 days. On the eleventh day one of them had a slightly positive sodium balance and the other went into labor (from our viewpoint, a deplorable propensity of pregnant women). The cumulative net loss of sodium in one patient was 665 mEq. in 10 days; in the other, the total net loss was 405 mEq. Their weight losses were 5.0 and 4.1 kilograms and their potassium gains were 262 and 158 mEq., respectively. The major losses in weight and sodium occurred in the first 6 days.

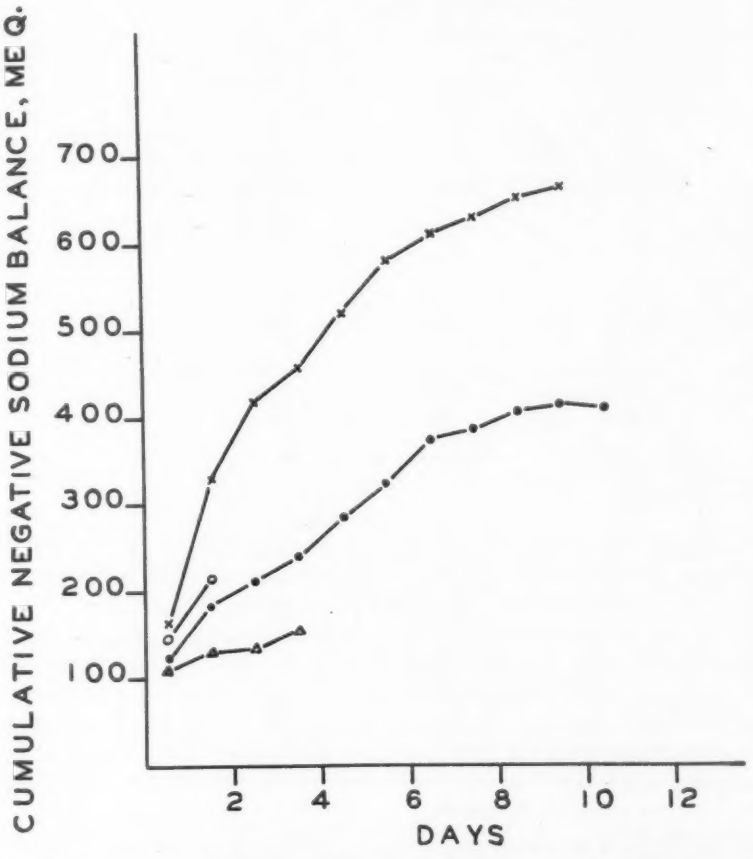

Fig. 1.—The cumulative negative sodium balances in pregnant edematous women whose only treatment was bed rest and dietary sodium restriction.

The data for the 7 pregnant women used in the evaluation of chlorothiazide are summarized in Table I. All had lost weight in the control period; in an average of 6 days, the mean weight loss was 2.8 kilograms. All were still in negative sodium balance when treatment with chlorothiazide was begun, i.e., bed rest and sodium restriction were still having an effect, which was marked in Cases 5 and 6. Ideally, the study should have begun only after sodium balance was attained, but in pregnancy this ideal is hard to realize for at this point the edema would be gone.

Table I shows the changes that occurred by the end of 6 days of therapy with 1 Gm. of chlorothiazide per day. All patients lost weight, although the loss was not impressive in 4 of the 7 cases. The net sodium losses, based upon an assumed daily intake of 30 mEq., averaged 412 mEq. (range 110 to 671). The losses in exchangeable sodium were somewhat greater (mean 560 mEq.). Part of the reason for this is that the assumption of a daily intake of 30 mEq. of sodium made no allowance for rejection of food, although this cannot account for all of the discrepancy. The average daily loss of sodium was 70 mEq., as estimated from the urinary excretion data, and 93 mEq. as calculated from losses in exchangeable sodium. In the 24 hour control period immediately preceding the first dose of chlorothiazide, the sodium loss averaged 68 mEq., but this would have decreased daily in the absence of drug therapy.

TABLE I. SOME EFFECTS OF BED REST AND SALT RESTRICTION AND OF CHLOROTHIAZIDE IN PREGNANT WOMEN

		CONTROL PERIOD			SIX DAYS ON CHLOROTHIAZIDE THERAPY				
						SODIUM LOSS			
CASE*	DIAGNOSIS	DAYS IN HOSPITAL	WEIGHT LOSS (KG.)	24 HOUR SODIUM BALANCE† (mEq.)	WEIGHT LOSS (KG.)	BALANCE† (mEq.)	EXCHANGEABLE (mEq.)	PLASMA VOLUME LOSS (ML.)	POTASSIUM BALANCE† (mEq.)
1 ●	Pre-eclampsia	5	4.0	−40	1.2	110	595	--	+166
2 ×	Hypertension	5	1.8	−24	1.1	177	310	90	−54
3 ○	Hypertension	10	2.2	−28	0.2	239	300	210	+108
4 △	Nephrotic stage of glomerulonephritis	7	2.2	−16	1.5	671	770	195	+51
5 □	Hookworm with edema	5	4.2	−144	3.2	631	825	1070	+238
6 ▽	Hypertension	5	3.3	−151	4.6	584	--	--	+162
7 -	Hypertension	4	1.6	−75	4.4	469	--	820	+286
Means		6	2.8	−68	2.3	412	560	477	+139

*With symbols used to denote cases in Fig. 2.
†Estimates (see text).

The 4 hour sodium space decreased by an average of 2.8 L. as compared to the average weight loss of 2.3 kilograms. The plasma volume decreased in all 5 patients in whom it was measured, the mean drop being 477 ml.

Fig. 2 shows the daily excretions of sodium. In the one patient with preeclampsia the drug had little, if any, effect for in no day on the drug did she excrete as much sodium as in the control day before starting therapy. The curves for the other 6 patients are similar to each other: the maximal excretion of sodium occurred during the first day on chlorothiazide. Thereafter the effect of the drug was progressively less, day by day. On the sixth day, 2 of the patients were in positive sodium balance.

When chlorothiazide was discontinued, all patients observed further (5) went into positive sodium balance (rebound phenomenon). From the sharp drop in sodium excretion, it appears that the drug had had some effect, though slight, on the last day that it was given. The 3 patients in whom chlorothiazide was restarted, after 3 days off the drug, again responded with natriuresis.

The sodium and chloride excretions rose and fell together, and were almost equimolar during chlorothiazide therapy. The average ratio of sodium:chloride was 0.962, with a standard deviation of 0.033. Case 2, with essential hypertension, had an unusually low sodium:chloride ratio that averaged 0.71. This patient had only a transient natriuresis on the drug and was in positive sodium balance by the fifth day.

The effect of chlorothiazide upon potassium excretion was inconstant. In 42 days of observation (7 patients, each on the drug for 6 days), the potassium excretion was increased over control values in 20, decreased in 18, and the same in 4. There was no correlation between sodium and potassium excretions ($r = 0.20$). The serum potassium concentrations did not change significantly in any patient and the estimated potassium balance was positive in all but one.

Compared to the control 24 hour urine volume, the urine output remained the same (± 200 ml.) in 10 of the 42 treatment days, increased in 11, and decreased in 21. When chlorothiazide therapy was stopped, the urine volume remained the same in 2 cases and decreased in 3. The increased natriuresis induced by the chlorothiazide was associated with increased concentrations of sodium in the urine in every observation.

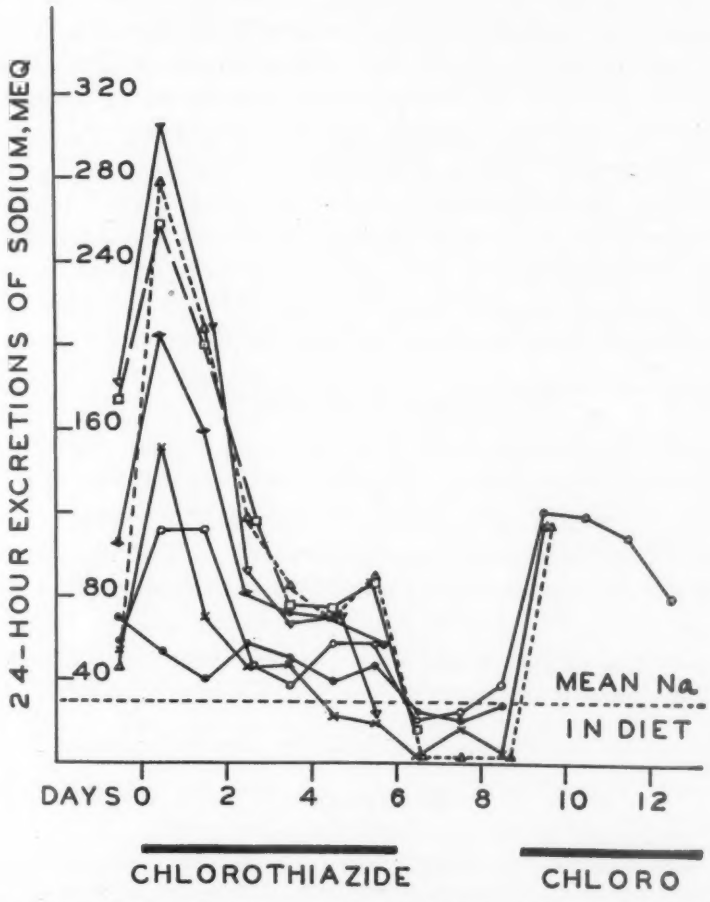

Fig. 2.—Daily sodium excretion in 7 pregnant edematous women. The first observation, in each case, was made before drug therapy and on the third to the ninth hospital day. Note that in 6 days on chlorothiazide the sodium excretion decreased from day to day. Patients identified by symbols in Table I.

Comment

We have not studied nonpregnant edematous patients and cannot make any direct comparisons, but chlorothiazide seems to be less effective in pregnant edematous women than it is alleged to be in other patients. This seems to be an almost general observation on the effects of diuretic drugs, for Assali,

Herzig, and Singh[6] found ammonium chloride to be less potent in causing salt loss in toxemic women than in others. Dieckmann[7] wrote that the same is true of mercurial diuretics.

Chlorothiazide increased the sodium excretion in 6 of the 7 patients studied, although the effect decreased progressively from day to day, i.e., drug resistance developed within a few days, as Fig. 2 clearly shows. When the drug was restarted, after a 3 day rest, natriuresis again occurred in the 3 patients studied in this way.

The one patient in whom chlorothiazide was ineffective was the only one in the series with pre-eclampsia. One case does not prove that patients with pre-eclampsia are refractory to the drug. Actually, we have observations in 2 other women with preeclampsia. In one, the sodium excretion in the 24 hour control period was 28.2 mEq. In the first day on the drug (sixth hospital day) no more than two-thirds of the urine output was saved, as judged from the creatinine excretion, but the measured sodium output was 75 mEq. In the next 3 days, with complete urine collections, the sodium excretions were 125, 101, and 86.8 mEq. The other patient had severe pre-eclampsia and was started on chlorothiazide as soon as a control 24 hour urine specimen had been obtained. On the control day, she excreted 42.7 mEq. of sodium and in 3 days on the drug the sodium excretion was 142, 117, and 50.9 mEq. Thus, 2 of the 3 pre-eclamptic patients did respond to the drug with natriuresis.

Summary and Conclusions

In pregnant edematous women, bed rest and dietary sodium restriction alone have a good diuretic effect. Negative sodium balances are maintained for several days (10 days in the 2 patients followed that long).

Chlorothiazide stimulates sodium and chloride excretion in pregnant edematous women, after the major effect of bed rest and a low-sodium diet has occurred.

Resistance to chlorothiazide develops progressively from day to day. It seems to disappear after a rest period of 3 days (possibly less)

We are grateful to Mrs. Barbara Mendelsohn for technical assistance.

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THE WORK AND FORCE OF DIGITAL VASOCONSTRICTION IN NORMOTENSIVE AND HYPERTENSIVE PREGNANT WOMEN*

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IN A previous study,[1] flow and pressure in the digital circulation were measured in a series of normotensive and hypertensive subjects. From these data radius equivalents of the digital circulation could be calculated: (1) at rest, at room temperature between 26° and 29° C.; and (2) after inhibition of sympathetic nerve discharge by indirect heating supplemented by the intravenous administration of a ganglion-blocking drug. These radius equivalents and the pressures were used to calculate the work and mean force of vasoconstriction, as well as the per cent work index or percentage of maximal potential work represented by the actual work of vasoconstriction.

These methods were used to study a series of 16 normotensive pregnant women in the third trimester of pregnancy compared with a series of 16 hypertensive pregnant women also in the third trimester of pregnancy. Flow was measured calorimetrically, brachial pressure with the cuff method, and digital pressure with a Gärtner capsule.[2] The venous pressure correction was estimated according to a schema by which the correction decreases in proportion to decreasing flow as influenced either by vasoconstriction or by decreasing pressure head. Effective mean digital arterial pressure after vasodilatation was diastolic plus one third of pulse pressure minus the venous pressure correction. Effective mean digital arterial blood pressure before vasodilatation was diastolic plus one third of pulse pressure minus the venous pressure correction and minus the calculated pressure axis intercept of the flow-pressure relationship for the degree of vasoconstriction represented by that relationship. The radius equivalents of the digital circulation in the dilated and in the resting or constricted state were then calculated. The rationale and formulas for calculating work, work index, and force of vasoconstriction from these data have been presented previously.[1]

Room temperature in these studies was always between 26 and 29° C. and the patients were recumbent in bed with standard covering. To achieve maximal vasodilatation, indirect heat was applied with a cradle baker over the

*Aided by grants from the National Heart Institute (H1164-C3 and 4) and the American Heart Association.

TABLE I. STATISTICAL ANALYSIS OF CHANGE IN THE DIGITAL CIRCULATION BEFORE (B) AND AFTER (A) VASODILATATION WITH INDIRECT HEAT AND CHEMICAL AUTONOMIC GANGLION BLOCKADE IN 16 NORMOTENSIVE (N_1) AND 16 HYPERTENSIVE (H_1) WOMEN IN THE THIRD TRIMESTER OF PREGNANCY

VALUE	GROUP	PHASE	RANGE	MEAN	STANDARD ERROR OF DIFFERENCE	PROBABILITY THAT DIFFERENCE IS DUE TO CHANCE
Brachial systolic blood pressure (mm. Hg)	N_1	A	76-114	95.0		
	H_1	A	86-140	113.0	4.2	$<10^{-4}$
	N_1	B	96-128	112.0		
	H_1	B	111-161	136.0	3.7	$<10^{-9}$
Brachial diastolic blood pressure (mm. Hg)	N_1	A	47-81	64.0		
	H_1	A	72-114	75.0	3.1	$<10^{-2}$
	N_1	B	53-87	70.0		
	H_1	B	62-106	84.0	3.5	$<10^{-4}$
Digital systolic blood pressure (mm. Hg)	N_1	A	64-118	91.0		
	H_1	A	56-136	96.0	6.0	<0.5
	N_1	B	83-129	106.0		
	H_1	B	90-152	121.0	4.8	$<10^{-2}$
Digital diastolic blood pressure (mm. Hg)	N_1	A	32-84	58.0		
	H_1	A	33-91	62.0	4.9	<0.4
	N_1	B	48-88	68.0		
	H_1	B	58-88	73.0	3.1	<0.2
Brachial-digital systolic pressure gradient (mm. Hg)	N_1	A	-21-30	4.4		
	H_1	A	-7-40	17.0	4.3	$<10^{-2}$
	N_1	B	-22-33	5.8		
	H_1	B	-8-42	17.0	4.6	$<10^{-1}$
Brachial-digital diastolic pressure gradient (mm. Hg)	N_1	A	-20-32	6.3		
	H_1	A	-15-41	13.0	4.7	<0.2
	N_1	B	-26-27	1.1		
	H_1	B	-7-33	12.0	4.3	$<10^{-2}$
Effective mean digital blood pressure (mm. Hg)	N_1	A	32-80	56.0		
	H_1	A	28-90	59.0	5.0	<0.5
	N_1	B	46-90	68.0		
	H_1	B	55-97	76.0	3.8	$<10^{-1}$
Calculated pressure axis intercept of flow-pressure relationship (mm. Hg)	N_1	B	0-27	12.0		
	H_1	B	3-25	14.0	2.0	<0.4
Digital blood flow (cm.^{3}/cm.^{2} skin/minute)	N_1	A	0.19-0.47	0.33		
	H_1	A	0.23-0.47	0.35	0.077	<1.0
	N_1	B	0.15-0.43	0.29		
	H_1	B	0.17-0.41	0.29		
Radius equivalent of digital blood vessels (10^{-2} cm.)	N_1	A	2.6-3.8	3.2		
	H_1	A	2.6-3.7	3.2		
	N_1	B	2.6-3.6	3.1		
	H_1	B	2.6-3.4	3.0	0.08	<0.2
Difference in radius equivalents (10^{-2} cm.)	N_1		0.10-0.39	0.16		
	H_1		0.04-0.44	0.20	0.045	<1.0
Maximum work of vasoconstriction (10^3 ergs)	N_1		8-16	12.0		
	H_1		9-17	13.0	0.75	<0.3
Work of vasoconstriction (10^3 ergs)	N_1		0.0-1.6	0.69		
	H_1		0.01-2.0	0.99	0.15	$<10^{-1}$
Work index (%)	N_1		3.1-16.7	6.3		
	H_1		1-15	7.3	1.5	<0.5
Force of vasoconstriction (10^4 dynes)	N_1		31-61	46.0		
	H_1		30-74	52.0	4.0	<0.2

trunk for one half hour or more until diaphoresis was diffuse. Then 0.8 mg. per kilogram of a ganglion-blocking quaternary amine, 2, 6 dimethyl-1, 1-diethyl piperidinium bromide (SC 1950) was injected intravenously. Although a few patients developed postural hypotension, for which the foot of the bed had to be elevated, there were no serious untoward effects of the procedure.

Most of the patients fell clinically into the group with pre-existing primary hypertension but no attempt was made to separate these cases in the statistical analysis from cases of so-called "pure" toxemia. It was felt that some of the latter were probably also unrecognized cases of primary hypertension. Patients with overt renal disease or complicating metabolic diseases such as hyperthyroidism or diabetes mellitus were not included in this study.

Results

It is apparent from Table I that the only difference between the normal and hypertensive pregnant groups was increased neurogenic vasoconstriction in the hypertensive group, although only to the $p<10^{-1}$ index of confidence. This was manifested by increased work of vasoconstriction in the hypertensive patients. There was no significant difference in the caliber after vasodilatation in the two groups, indicating that, in this group of hypertensive pregnant patients, such hypertension as existed was mild and not advanced, since a decrease in this caliber is a feature of advancing essential hypertension.[1] The increase in mean force of vasoconstriction in the hypertensive patients was a direct manifestation of the elevated blood pressure itself. The only other factor that could influence this value is a change in caliber after vasodilatation and there was no significant difference between the two groups in this respect. There was also a significantly greater systolic as well as diastolic brachial-digital arterial pressure gradient in the hypertensive group both before and after vasodilatation, whereas, when normal nonpregnant patients were compared with hypertensive nonpregnant patients, there was no consistent pattern of change (Table II).

TABLE II. STATISTICAL ANALYSIS OF CHANGE IN THE BRACHIAL-DIGITAL PRESSURE GRADIENTS BEFORE (B) AND AFTER (A) VASODILATATION WITH INDIRECT HEAT AND CHEMICAL AUTONOMIC BLOCKADE IN 23 NORMOTENSIVE (N_2) AND 36 HYPERTENSIVE (H_2) SUBJECTS

VALUE	GROUP	PHASE	RANGE	MEAN	STANDARD ERROR OF DIFFERENCE	PROBABILITY THAT DIFFERENCE IS DUE TO CHANCE
Brachial-digital systolic gradient (mm. Hg)	N_2	A	-1-35	17.0		
	H_2	A	-24-37	11.0	3.0	$<10^{-1}$
	N_2	B	-4-32	14.0		
	H_2	B	-15-72	28.0	4.1	$<10^{-3}$
Brachial-digital diastolic gradient (mm. Hg)	N_2	A	-6-30	12.0		
	H_2	A	-22-44	11.0	3.3	<1.0
	N_2	B	-21-31	4.7		
	H_2	B	-27-51	12.0	4.2	$<10^{-1}$

In comparing data from normal pregnant women with data from normal subjects not pregnant (Table III), it is apparent that there is a significant decrease in brachial systolic pressure in the pregnant group, although not in diastolic pressure or in digital systolic or diastolic pressure. The brachial-digital systolic gradient is significantly decreased in pregnancy both before and

TABLE III. STATISTICAL ANALYSIS OF CHANGE IN THE DIGITAL CIRCULATION BEFORE (B) AND AFTER (A) VASODILATATION WITH INDIRECT HEAT AND CHEMICAL AUTONOMIC BLOCKADE IN 16 NORMOTENSIVE (N_1) WOMEN IN THE THIRD TRIMESTER OF PREGNANCY COMPARED WITH 23 NORMOTENSIVE (N_2) SUBJECTS

VALUE	GROUP	PHASE	RANGE	MEAN	STANDARD ERROR OF DIFFERENCE	PROBABILITY THAT DIFFERENCE IS DUE TO CHANCE
Brachial systolic blood pressure (mm. Hg)	N_1	A	76-114	95.0		
	N_2	A	85-123	104.0	3.1	$<10^{-2}$
	N_1	B	96-128	112.0		
	N_2	B	96-140	118.0	3.0	$<10^{-1}$
Brachial diastolic blood pressure (mm. Hg)	N_1	A	47-81	64.0		
	N_2	A	51-79	65.0	2.6	<1.0
	N_1	B	53-87	70.0		
	N_2	B	52-88	70.0		
Digital systolic blood pressure (mm. Hg)	N_1	A	64-118	91.0		
	N_2	A	67-107	87.0	4.0	<0.4
	N_1	B	83-129	106.0		
	N_2	B	70-138	104.0	4.5	<1.0
Digital diastolic blood pressure (mm. Hg)	N_1	A	32-84	58.0		
	N_2	A	32-72	52.0	4.0	<0.2
	N_1	B	48-88	68.0		
	N_2	B	39-91	65.0	3.7	<0.5
Brachial-digital systolic pressure gradient (mm. Hg)	N_1	A	-21-30	4.4		
	N_2	A	-1-35	17.0	3.7	$<10^{-3}$
	N_1	B	-22-33	5.8		
	N_2	B	-4-32	14.0	3.9	$<10^{-1}$
Brachial-digital diastolic pressure gradient (mm. Hg)	N_1	A	-20-32	6.3		
	N_2	A	-4-30	12.0	3.9	<0.2
	N_1	B	-26-27	1.1		
	N_2	B	-21-31	4.7	4.4	<0.5
Effective mean digital blood pressure (mm. Hg)	N_1	A	32-80	56.0		
	N_2	A	34-70	52.0	3.7	<0.3
	N_1	B	46-90	68.0		
	N_2	B	42-98	70.0	4.0	<1.0
Calculated pressure axis intercept of flow-pressure relationship (mm. Hg)	N_1	B	0-27	12.0		
	N_2	B	12-26	17.0	1.9	$<10^{-2}$
Digital blood flow ($cm.^3$/ $cm.^2$ skin/minute)	N_1	A	0.19-0.47	0.33		
	N_2	A	0.21-0.37	0.29	0.034	<0.3
	N_1	B	0.15-0.43	0.29		
	N_2	B	0.08-0.32	0.20	0.022	$<10^{-4}$
Radius equivalent of digital blood vessels (10^{-2} cm.)	N_1	A	2.6-3.8	3.2		
	N_2	A	2.9-3.7	3.3	0.083	<0.3
	N_1	B	2.6-3.6	3.1		
	N_2	B	2.5-3.3	2.9	0.074	$<10^{-2}$
Difference in radius equivalents (10^{-2} cm.)	N_1		0.10-0.39	0.16		
	N_2		0.10-0.70	0.40	0.045	$<10^{-6}$
Maximum work of vasoconstriction (10^3 ergs)	N_1		8-16	12.0		
	N_2		10-14	12.0		
Work of vasoconstriction (10^3 ergs)	N_1		0.25-1.6	0.69		
	N_2		0.30-3.1	1.7	0.19	$<10^{-6}$
Work index (%)	N_1		0-16	6.3		
	N_2		2-28	15.0	1.8	$<10^{-6}$
Force of vasoconstriction (10^4 dynes)	N_1		31-61	46.0		
	N_2		31-53	42.0	2.2	$<10^{-1}$

TABLE IV. STATISTICAL ANALYSIS OF CHANGE IN THE DIGITAL CIRCULATION BEFORE (B) AND AFTER (A) VASODILATATION WITH INDIRECT HEAT AND CHEMICAL AUTONOMIC BLOCKADE IN 16 HYPERTENSIVE (H_1) WOMEN IN THE THIRD TRIMESTER OF PREGNANCY COMPARED WITH 36 HYPERTENSIVE (H_2) PATIENTS

VALUE	GROUP	PHASE	RANGE	MEAN	STANDARD ERROR OF DIFFERENCE	PROBABILITY THAT DIFFERENCE IS DUE TO CHANCE
Brachial systolic blood pressure (mm. Hg)	H_1	A	86-140	113.0		
	H_2	A	83-179	131.0	5.3	$<10^{-3}$
	H_1	B	111-161	136.0		
	H_2	B	156-236	196.0	4.6	Infinitesimal
Brachial diastolic blood pressure (mm. Hg)	H_1	A	54-96	75.0		
	H_2	A	49-121	85.0	3.9	$<10^{-2}$
	H_1	B	62-106	84.0		
	H_2	B	89-141	115.0	3.5	Infinitesimal
Digital systolic blood pressure (mm. Hg)	H_1	A	56-136	96.0		
	H_2	A	74-166	120.0	6.3	$<10^{-4}$
	H_1	B	90-152	121.0		
	H_2	B	113-223	168.0	6.0	Infinitesimal
Digital diastolic blood pressure (mm. Hg)	H_1	A	33-91	62.0		
	H_2	A	38-112	75.0	4.7	$<10^{-2}$
	H_1	B	58-88	73.0		
	H_2	B	55-151	103.0	4.4	$<10^{-11}$
Brachial-digital systolic gradient (mm. Hg)	H_1	A	-7-40	17.0		
	H_2	A	-24-37	11.0	4.2	<0.2
	H_1	B	-8-42	17.0		
	H_2	B	-15-72	28.0	4.7	$<10^{-1}$
Brachial-digital diastolic gradient (mm. Hg)	H_1	A	-15-41	13.0		
	H_2	A	-22-44	11.0	4.4	<1.0
	H_1	B	-7-33	12.0		
	H_2	B	-27-51	12.0		
Effective mean digital blood pressure (mm. Hg)	H_1	A	28-90	59.0		
	H_2	A	42-114	78.0	4.9	$<10^{-4}$
	H_1	B	55-97	76.0		
	H_2	B	72-162	117.0	4.6	Infinitesimal
Calculated pressure axis intercept of flow-pressure relationship (mm. Hg)	H_1	B	3-25	14.0		
	H_2	B	1-78	40.0	3.5	Infinitesimal
Digital blood flow (cm.^{3}/cm.^{2} skin/minute)	H_1	A	0.23-0.47	0.35		
	H_2	A	0.21-0.41	0.31	0.018	$<10^{-1}$
	H_1	B	0.17-0.41	0.29		
	H_2	B	0.02-0.34	0.18	0.02	$<10^{-7}$
Radius equivalent of digital blood vessels (10^{-2} cm.)	H_1	A	2.6-3.7	3.2		
	H_2	A	2.6-3.4	3.0	0.08	$<10^{-1}$
	H_1	B	2.6-3.4	3.0		
	H_2	B	1.9-3.1	2.5	0.074	Infinitesimal
Difference in radius equivalents (10^{-2} cm.)	H_1		0.04-0.44	0.20		
	H_2		0.07-0.99	0.53	0.048	$<10^{-10}$
Maximum work of vasoconstriction (10^3 ergs)	H_1		9-17	13.0		
	H_2		10-20	15.0	0.7	$<10^{-2}$
Work of vasoconstriction (10^3 ergs)	H_1		0.01-2.0	0.99		
	H_2		0.10-6.9	3.5	0.31	Infinitesimal
Work index (%)	H_1		1-15	7.3		
	H_2		0-48	24.0	2.2	Infinitesimal
Force of vasoconstriction (10^4 dynes)	H_1		30-74	52.0		
	H_2		40-86	63.0	3.3	$<10^{-3}$

after vasodilatation, whereas the diastolic gradient is not significantly different. The major effect, however, is increased digital blood flow prior to vasodilatation in the pregnant group. This becomes manifest as a significantly greater vascular caliber prior to vasodilatation in the pregnant group as well as a lesser change in caliber with vasodilatation, since the vascular caliber in the two groups after vasodilatation is nearly the same. Hence the work of vasoconstriction is significantly decreased in the pregnant group, as is work index.

Similar differences are apparent if the hypertensive pregnant patient is compared with the nonpregnant hypertensive patient (Table IV). It must be remembered here that the hypertension is more advanced in the nonpregnant group. This is apparent from the significantly decreased vascular caliber after vasodilatation and the significantly higher blood pressure in both phases of the procedure in the nonpregnant group. The gradients on the other hand show no significant trend here. There is also greater blood flow before vasodilatation, a greater vascular caliber in this phase, and a smaller difference in caliber between the two phases of vasodilatation and vasoconstriction in the hypertensive pregnant group when compared with the hypertensive nonpregnant group. There is hence less work and force of vasoconstriction and a smaller work index in the hypertensive pregnant than in the hypertensive nonpregnant group. How much of this effect is caused by pregnancy and how much by the mildness of the hypertension in the pregnant group is conjectural, although it is likely that both factors are additive.

Comment

From the data presented, neurogenic vasoconstriction seems increased in the digital circulation in the hypertension of pregnancy. Since this is considered to be the hallmark of primary or essential hypertension, one may reason that patients with so-called "toxemia" of pregnancy may well be patients with overt or latent primary hypertension.

The effect of pregnancy itself on the digital circulation is the same as that of any factor which increases heat production. It decreases the vasoconstriction produced by any given room temperature.[3] This is seen in the normotensive as well as the hypertensive group but is unequivocal only in the former. The terms basal metabolism and hyperthyroidism had best be avoided in this respect, since it is not known how much of this effect is due to increased production of thyroid hormone[4] and how much to such factors as increased work of breathing or increased metabolism due to the metabolic contributions of the placenta, fetus, and enlarged uterus.

Another significant effect of normal pregnancy is a decrease in the brachial-digital systolic pressure gradient. This effect cannot, however, be clearly demonstrated in the hypertensive pregnant group when compared with the hypertensive nonpregnant group. The gradient in the hypertensive pregnant group, on the other hand, is greater than in the normotensive pregnant group. The meaning of this gradient change is obscure. It must be remembered that brachial and digital pressures are not measured simultaneously, so that phasic changes may play a role in the gradient and may often make it appear negative. In the vasodilated state, moreover, increasing and decreasing effect of the ganglion-blocking drug may affect the estimation of the gradient. These

technical factors, however, were similar in all groups. The major physiologic factors affecting gradient are: (1) the caliber of the vessels in a direct line between brachial and digital arteries, and (2) the amount of runoff to intervening tissues, especially muscle. The latter is in turn proportional to the height of the brachial blood pressure. Since the arteries are apparently dilated by pregnancy, this factor as well as the decrease in brachial arterial pressure may account for the decreased gradient. Muscle blood flow has been found to be normal[5] in pregnancy and increased[6] in the hypertension of pregnancy.

Summary

1. Arterial pressure and flow were measured in the digital circulation both before and after vasodilatation in normotensive and hypertensive pregnant women in the third trimester. The work, work index, and force of vasoconstriction and caliber changes were calculated from the data.

2. There was some increase in neurogenic vasoconstriction in the hypertensive group.

3. Pregnancy itself tended to decrease neurogenic vasoconstriction in both groups, probably because of increased heat production. Normal pregnancy, moreover, tended to decrease the brachial-digital systolic pressure gradient.

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STUDIES OF CHOLINESTERASE ACTIVITY

IV. Liver Function in Pregnancy: Values of Certain Standard Liver Function Tests in Normal Pregnancy*†

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A STUDY of cholinesterase activity in pregnancy indicated that available data pertaining to liver function in pregnant women have been somewhat limited in scope and, often, of contradictory nature. Therefore, it was found necessary to re-evaluate certain liver function tests in a group of normal women in various stages of pregnancy in order to establish significant mean values for our laboratory. Following this, a comparison with mean values in abnormal pregnancies could be made.

This paper gives the results of studies performed on maternal serum during pregnancy and on placental vein serum (fetal blood) at delivery. Tests described include serum total cholesterol, serum cholesterol esterification, serum alkaline phosphatase, serum bilirubin, serum total protein, serum albumin, serum globulin, serum thymol turbidity, serum cephalin flocculation, serum cholinesterase activity, and hematocrit percentages. Results obtained by other groups are stated immediately preceding our results for the individual tests.

Methods

The patients were normal women observed during "normal" pregnancy. They were studied in an outpatient prenatal clinic and in the hospital at the time of delivery. Cases were selected consecutively, abnormal pregnancies being excluded at the completion of the study. Results are for groups of women at various stages of pregnancy. Serial studies in the same women were not attempted. Prenatal care included supplementary multivitamins, iron, and calcium.

A "normal" pregnancy was defined as one free of hypertension, edema, unusual weight gain, significant albuminuria, or any concurrent organic disease. All patients had benign past histories and remained normal in all respects during the period of observation.

Blood samples were collected by venipuncture in the nonfasting state. Fetal samples obtained directly from the cord were often unsatisfactory technically because of hemolysis. Therefore, the fetal sample was obtained from

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one of the large placental vessels immediately after expression of the placenta. These samples were not hemolyzed or clotted and gave values comparable to samples from the cord itself.

The testing methods used were as follows:

1. *Serum total cholesterol and cholesterol esters*
   Method of Schoenheimer and Sperry[1]
   Normal: Total cholesterol, 150-300 mg. per cent
   Cholesterol ester (percentage of total), 65-75 per cent
2. *Serum alkaline phosphatase*
   Method of Roe and Whitmore[2]
   Normal: Up to 5.0 Bodansky units
3. *Serum proteins, albumin, and globulin*
   Method of Kingsley[3]
   Normal: Total protein, 6.0-8.0 Gm. per cent
   Normal: Albumin, 3.8-5.5 Gm. per cent
   Globulin, 2.0-3.5 Gm. per cent
4. *Serum bilirubin, total and direct*
   Method of Malloy and Evelyn[4]
   Normal: Total, up to 1.0 mg. per cent
   Direct, up to 0.2 mg. per cent
5. *Serum thymol turbidity*
   Method of Shank and Hoagland[5]
   Normal: Up to 4.0 units
6. *Serum cephalin flocculation*
   Method of Hanger[6]
   Normal: Zero and one plus in 48 hours considered normal
   Two plus in 48 hours is considered borderline
7. *Serum cholinesterase activity*
   Method of de la Huerga, Yesinick, and Popper[7]
   Normal: 150-305 units. Mean of 212 units (204 fasting, 220 non-fasting)[33]
8. *Hematocrit* (Microhematocrit technique of Guest-Siler[8, 9])

Results

A. Serum Total Cholesterol.—Cholesterol has been reported to be increased in normal pregnancy. Dieckmann and Wegner[10] give the following ranges of values: 10 to 15 weeks, 113 to 427 mg. per cent; 26 to 35 weeks, 181 to 335 mg. per cent; and 36 weeks to term, 137 to 525 mg. per cent. Gardner and Gainsborough[11] stated that the maximal increase in cholesterol is reached at about the thirtieth week of pregnancy after which it diminishes before delivery. Popper and Schaffner,[12] however, report that hypercholesterolemia occurs in the last trimester of pregnancy. Cholesterol mean elevation is reported from about 10 per cent[13] to 50 to 100 per cent.[11]

Present results demonstrated that serum total cholesterol was increased during pregnancy, reaching a peak mean value at the time of labor (Table I). During active labor nearly three fourths of the mothers had levels in excess of 300 mg. per cent and about one fourth exceeded 400 mg. per cent.

Comparison of placental blood with maternal samples revealed that the mean fetal cholesterol level was 228 mg. per cent less than that of the corresponding mothers (Table II). In 46 of 48 instances the maternal values

exceeded the fetal values. There was no direct correlation between maternal and fetal levels, values being generally low in the fetal sample regardless of maternal values. Moreover, the lower maternal values were not necessarily associated with lower fetal values.

TABLE I. SERUM TOTAL CHOLESTEROL IN MATERNAL BLOOD DURING NORMAL PREGNANCY

STAGE	NO. OF CASES	MEAN CHOLESTEROL IN MG. %*	RANGE	NO. > 300 MG. %	NO. > 400 MG. %
First trimester	9	173	134-238	0	0
Second trimester	10	239	158-284	0	0
Third trimester	11	310	214-435	6	1
Labor	69	350	214-555	51	17

*Normal range, 150-300 mg. per cent.

TABLE II. SERUM TOTAL CHOLESTEROL: COMPARISON OF 48 MATERNAL SAMPLES DURING LABOR WITH THE CORRESPONDING FETAL BLOODS

SAMPLE	MEAN CHOLESTEROL (MG. %)	STANDARD DEVIATION	RANGE	NO. > 300 MG. %	NO. > 400 MG. %
Maternal*	345	±61.9	247-542	35	10
Fetal	117	±66.3	50-450	2	1

*In 46 of 48 comparisons, maternal values exceeded fetal values.

B. Serum Cholesterol Esters.—Cantarow and Trumper[13] stated that the average increment during pregnancy in free cholesterol is about 25 per cent and that of the ester fraction about 5 per cent. On the other hand, Bloor and Knudson[14] claimed that the ester fraction increases more than does the free fraction. Boyd[15] reported normal ester percentages at term. Gardner and Gainsborough[11] indicated that only the total free cholesterol rises and that the esters fall during pregnancy.

Our studies have demonstrated that the cholesterol ester fraction was essentially normal throughout pregnancy (Table III). Comparison of mean values for placental blood with those for maternal serum collected during labor revealed no significant differences (Table III). There was no direct correlation between individual maternal and fetal degrees of esterification.

TABLE III. SERUM CHOLESTEROL ESTERS IN MATERNAL BLOOD DURING NORMAL PREGNANCY WITH COMPARISON OF MATERNAL AND FETAL BLOOD AT DELIVERY

STAGE	NO. OF CASES	MEAN CHOLESTEROL ESTERS* (% OF TOTAL)	RANGE	NO. < 65 %
First trimester	9	71	63-75	1
Second trimester	10	65	47-75	3
Third trimester	11	71	67-75	0
Labor	25	69	62-74	2
Fetal†	25	67	46-75	6

*Normal range, 65 to 75 per cent.

†In 13 of 25 instances, fetal cholesterol esters were equal to or exceeded maternal values.

C. Serum Alkaline Phosphatase.—Alkaline phosphatase is stated to be increased during pregnancy,[16] values being elevated in 37 of 40 cases studied by Capps as reported by Long and associates.[17]

Current results have shown that serum alkaline phosphatase activity rose in the third trimester of pregnancy, reaching a peak mean value during active labor (Table IV). At this time nearly three fourths of the observed group of mothers had values in excess of 5.0 Bodansky units.

TABLE IV. SERUM ALKALINE PHOSPHATASE IN MATERNAL BLOOD DURING NORMAL PREGNANCY

STAGE	NO. OF CASES	MEAN ALKALINE PHOSPHATASE* (BODANSKY UNITS)	RANGE	NO. >5.0
First trimester	10	2.2	1.5-3.5	0
Second trimester	10	2.7	1.4-3.5	0
Third trimester	11	6.5	2.1-13.4	8
Labor	42	6.9	2.7-15.0	31

*Upper limit of normal range, 5.0 Bodansky units.

Comparison of maternal values with corresponding fetal values indicated that both groups had elevated alkaline phosphatase activity. The maternal mean value was higher than that of the placental bloods (Table V). This difference was not statistically valid, the standard error of the means being 1.6. There was no direct correlation between the individual fetal and maternal values.

TABLE V. SERUM ALKALINE PHOSPHATASE: COMPARISON OF 20 MATERNAL SAMPLES DURING LABOR WITH THE CORRESPONDING FETAL BLOODS

SAMPLE	MEAN ALKALINE PHOSPHATASE (BODANSKY UNITS)	RANGE	NO. >5.0
Maternal*	6.8	2.7-9.9	13
Fetal	5.9	3.8-8.2	15

*In 12 of 20 instances maternal levels exceeded fetal levels.

D. Serum Proteins.—According to Dieckmann[16] albumin ranges from 2.9 to 4.3 Gm. per cent and lobulin from 2.3 to 3.8 Gm. per cent during normal pregnancy. Dieckmann and Wegner[10] reported total protein ranges as follows: 10 to 15 weeks of pregnancy, 5.9 to 7.5 Gm. per cent; 26 to 35 weeks, 5.6 to 7.2 Gm. per cent; and 36 weeks to term, 5.7 to 7.3 Gm. per cent. Results for "late normal pregnancy" were 5.0 to 7.2 Gm. per cent. At labor, values were 6.4 to 7.0 Gm. per cent in maternal blood; 5.3 to 6.7 Gm. per cent in cord blood, according to Oberst and Plass.[18] Cantarow and Trumper[13] reported a steady decrease in albumin levels during pregnancy but stated that subnormal values were rare. Mack and co-workers[19] stated that low albumin with high globulin is associated with pregnancy. Total plasma protein was said to decrease about 13 per cent during pregnancy with a trend toward low albumin and gamma globulin and higher alpha-1, alpha-2, and beta globulins.[20] Plass and Matthew,[21] reporting on 15 maternal and fetal values, found a mean total protein of 6.7 Gm. per cent in mothers, 5.9 Gm. per cent in infants. Using microchemical analytic technique, Mack and his associates[22] found a mean total protein of 6.0 Gm. per cent in 208 white women in the ninth month of normal pregnancy, and 6.2 Gm. per cent in 193 Negro women in the corresponding stage of pregnancy. It has been shown[23] that fetal alpha-2 and beta globulin combined is less than one half the maternal value.

The present studies indicated a fall in total protein of about 1 Gm. per 100 c.c. from the first to the third trimester of pregnancy. A decrease in albumin accounted for about two thirds of the fall and that of globulin for the remainder (Table VI). Globulin values rose somewhat by the time of labor, however. Protein depression at that time was on the basis of lowered albumin only.

A comparison of materal values with corresponding fetal values indicated roughly equivalent albumin levels but a lower fetal total protein on the basis of a lower globulin value (Table VI). In 22 of 26 instances, maternal total protein

was higher than or equaled fetal total protein. Globulin values in maternal sera exceeded or equaled those for fetal sera in 24 of 26 comparisons. Fetal albumin levels, however, equaled or exceeded those of maternal blood in 20 of 26 examinations.

TABLE VI. SERUM TOTAL PROTEINS, ALBUMIN, AND GLOBULIN IN MATERNAL BLOOD DURING NORMAL PREGNANCY WITH COMPARISON OF MATERNAL AND FETAL BLOOD AT DELIVERY

STAGE	NO. OF CASES	MEAN TOTAL PROTEIN (GM./100 C.C.)	MEAN ALBUMIN (GM./100 C.C.)	MEAN GLOBULIN (GM./100 C.C.)
First trimester	10	7.9	4.9	3.0
Second trimester	9	6.9	4.3	2.6
Third trimester	11	6.8	4.2	2.6
Maternal*	25	7.2	4.3	2.9
Fetal	25	6.6	4.4	2.2

*In 22 of 25 instances, maternal total protein equaled (2 cases) or exceeded fetal values.
In 20 of 25 instances, fetal albumin equaled (2 cases) or exceeded maternal values.
In 24 of 25 instances, maternal globulin equaled (1 case) or exceeded fetal values.

E. Serum Thymol Turbidity.—Lichtman[24] reported thymol abnormalities in 15 per cent of normal pregnancies. Dieckmann gave mean values of 3.1 units in the first trimester, 2.7 in the second, and 2.9 in the third during normal pregnancy. The per cent abnormalities in the series were 15, 15, and 16, respectively.

Present studies have shown that thymol turbidity of maternal serum exceeded fetal levels in 25 of 26 corresponding samples. The maternal mean value at labor (2.6 units) was more than four times the fetal mean value (0.6 unit). However, the maternal mean value was not abnormal and only 4 of 26 values exceeded 4.0 units, the highest value being 5.7 units. All fetal values were normal with 1.6 units the maximum value. There was no direct correlation between fetal and maternal values.

F. Serum Bilirubin, Total and Direct.—Dieckmann and his associates, reporting on 85 normal pregnancies, gave the following bilirubin values: first trimester, 8 per cent abnormal; second trimester, 15 per cent abnormal; and third trimester, 20 per cent abnormal. Other observers[24] reported that 8 per cent of values may be abnormally elevated, one study[17] describing elevation of total bilirubin in 37 of 40 cases. Cord serum is said to average 1 to 2 mg./100 c.c. at birth.[25]

TABLE VII. SERUM BILIRUBIN-TOTAL IN MATERNAL BLOOD DURING NORMAL PREGNANCY

STAGE	NO. OF CASES	MEAN TOTAL BILIRUBIN (MG. %)	RANGE
First trimester	10	0.5	0.1-0.9
Second trimester	10	0.5	0.1-0.7
Third trimester	11	0.5	0.3-0.9
Labor	25	0.5	0.3-0.9

TABLE VIII. SERUM TOTAL AND DIRECT BILIRUBIN: COMPARISON OF 24 MATERNAL SAMPLES DURING LABOR WITH THE CORRESPONDING FETAL BLOODS

SAMPLE	MEAN TOTAL BILIRUBIN (MG. %)	RANGE	MEAN DIRECT BILIRUBIN (MG. %)	RANGE
Maternal	0.55	0.3-0.9	0.08	0.02-0.2
Fetal*	1.73	0.5-3.1	0.23	0.02-0.5

*In 22 of 24 instances, fetal total bilirubin exceeded maternal values.
In 19 of 24 instances, fetal direct bilirubin exceeded maternal values.

Present results revealed that serum total bilirubin was normal in maternal blood during normal pregnancy. No abnormal values were recorded (Table VII). Comparison of 24 maternal sera with corresponding fetal sera indicated higher total bilirubin in fetal blood. In 22 of 24 instances fetal total bilirubin exceeded maternal levels and in 19 of 24 instances fetal direct bilirubin levels were higher than maternal levels (Table VIII).

G. Serum Cephalin-Cholesterol Flocculation.—Lichtman[24] reported abnormal cephalin flocculation in 22.5 per cent of pregnant women. Salmon and Richman[26] found 10 of 15 jaundiced newborn infants had a two-plus abnormality, whereas 5 of 11 nonjaundiced newborns were similarly abnormal. No abnormality was found in 9 women from 6 to 8 months pregnant. Twenty-three of 65 normal women had two plus abnormality or greater at term. Of these, 13 were three plus or greater.

Present results demonstrate that cephalin flocculation was essentially within normal limits during pregnancy. Fetal results were similar (Table IX).

TABLE IX. SERUM CEPHALIN FLOCCULATION IN MATERNAL AND FETAL BLOOD DURING NORMAL PREGNANCY AND AT DELIVERY

STAGE	SAMPLE	NO. OF CASES	MAXIMUM 48 HOUR FLOCCULATION				
			0	1+	2+	3+	4+
First trimester	Maternal	10	7	1	1	1	0
Second trimester	Maternal	10	8	0	1	1	0
Third trimester	Maternal	11	9	1	1	0	0
Labor	Maternal	26	17	5	4	0	0
	Fetal	26	20	2	4	0	0

H. Serum Cholinesterase Activity.—Tourtellotte and Odell,[27] using a colorimetric method, demonstrated a fall in serum cholinesterase activity in pregnant women. The mean value in 19 nonpregnant women was 51.6 units, that in 50 pregnant women (most of them in the third trimester) was 41.5, and values averaging 33.4 were found in 19 toxemic women. No inhibitor or activator substances were discovered.

Pritchard,[28] using the Michel potentiometric method, reported as follows: in 34 nonpregnant women, mean value 0.84 units; in 13 first-trimester normal pregnancies, 0.80; in 44 second-trimester pregnancies, 0.72; in 49 third-trimester pregnancies, 0.66; and in 15 fetal bloods, 0.65. Postpartum values were normal. He explained the phenomenon of decreasing serum cholinesterase activity in terms of hemodilution. Pritchard and Weisman[29] also described red-blood-cell cholinesterase activity in normal pregnancy by the Michel method with a value of 0.81 units in women at delivery and 0.50 in their fetuses.

Our studies have shown maternal serum cholinesterase activity to be abnormally low as early as the first trimester of pregnancy. The fall continued until the third trimester (Table X). Comparison of maternal sera at the time of labor with corresponding placental blood samples revealed a slightly lower mean value in the fetal samples. In 44 of 61 instances, fetal serum cholinesterase activity was less than maternal values.

The mean serum cholinesterase of 51 white women in the second trimester was 160 units, as compared to a value of 157 units in 19 Negro women. In the third trimester 72 white women had a mean serum cholinesterase of 149 units, while 23 Negro women had a value of 147 units.

Women of gravidity i and ii had mean serum cholinesterase values of 158 units (26 cases) in the second trimester and 149 units (40 cases) in the third trimester of pregnancy, whereas similar values for gravidity iii and iv were 156 units (22 cases) and 147 units (23 cases), and those in gravidity v through x were 167 units (15 cases) and 158 units (24 cases), respectively.

TABLE X. SERUM CHOLINESTERASE ACTIVITY IN MATERNAL BLOOD DURING NORMAL PREGNANCY WITH COMPARISON OF MATERNAL AND FETAL BLOOD AT DELIVERY

STAGE	NO. OF CASES	MEAN CHOLINESTERASE ACTIVITY IN UNITS	STANDARD DEVIATION	RANGE	NO. <150 UNITS	% <150 UNITS
First trimester	17	175	±35.2	90-245	3	17.6
Second trimester	70	159	±39.4	35-250	23	32.9
Third trimester	95	148	±38.3	35-238	41	43.2
Labor	61	145	±40.2	48-258	29	47.5
Fetal*	61	130	±40.2	29-253	44	72.1
Postpartum	43	183	±35.1	118-278	3	7.0

*In 44 of 51 instances, fetal cholinesterase activity was less than maternal activity.

In mothers whose fetuses proved to be male, second-trimester mean cholinesterase was 159 units (26 cases) and third-trimester values were 145 units (43 cases). When the fetus was female, values were 161 units (33 cases) in the second trimester and 153 units (45 cases) in the third trimester.

When the fetal weight at birth was 4.6 to 7.2 pounds, maternal mean serum cholinesterase was 154 units (25 cases) in the second trimester and 152 units (42 cases) in the third trimester. Maternal values when fetal weights were 7.3 to 9.7 pounds were 166 units (29 cases) in the second trimester and 146 units (43 cases) in the third trimester.

There was no correlation between serum cholinesterase activity in individual mothers at the same stage of pregnancy with such factors as their race, the sex of the baby, the weight of the baby at birth, or their parity.

It is of interest that red cell cholinesterase activity was normal in maternal blood at delivery, whereas fetal blood showed low serum and low red-cell cholinesterase activity. In a comparison of 14 maternal-fetal samples, the mean maternal RBC cholinesterase activity was 1.10 Michel units as compared with 0.61 unit for fetal blood.

I. The Hematocrit of Maternal and Placental Blood, Relationship to Cholinesterase Activity.—Hematocrit ranges in normal pregnancy[10] are as follows: 10 to 15 weeks, 33 to 46 per cent; 26 to 35 weeks, 29 to 45 per cent; 36 weeks to term, 31 to 46 per cent; and 45 to 50 per cent in cord blood. In a study performed on fasting, resting subjects,[30] the results were: second trimester, 25 women, 35.8 per cent; third trimester, 42 women, 35.4 per cent; and last 4 weeks of third trimester, 17 women, 38.7 per cent.

Maternal values obtained in the present study are listed in Table XI. A comparison of maternal values during labor with corresponding fetal blood showed higher mean values in the fetus. In 21 of 27 comparisons, fetal hematocrit levels exceeded maternal hematocrit levels (Table XI).

TABLE XI. HEMATOCRIT OF MATERNAL BLOOD DURING NORMAL PREGNANCY WITH COMPARISON OF MATERNAL AND FETAL BLOOD AT DELIVERY

STAGE	NO. OF CASES	MEAN HEMATOCRIT	RANGE
First trimester	17	40.4	34-45
Second trimester	68	37.9	31-46
Third trimester	92	38.2	30-44
Labor	27	38.5	32-44
Fetal*	27	44.0	32-58
Postpartum	84	41.1	33-48

*In 21 of 27 instances, fetal hematocrit exceeded maternal values.

In pregnant women, disregarding trimester, a direct relationship between serum cholinesterase activity and hematocrit percentages was found (Table

XII). This did not account for the major part of the fall in cholinesterase activity, however, for the mean value for hematocrits in the normal range is below the normal mean cholinesterase value in nonpregnant women.

TABLE XII. COMPARISON OF MATERNAL HEMATOCRIT VALUES IN NORMAL PREGNANCY WITH CORRESPONDING SERUM CHOLINESTERASE ACTIVITY

HEMATOCRIT RANGE	NO. OF CASES	MEAN CHOLINESTERASE
31-37	56	147
38-39	61	159
40-48	80	170

Comment

In contrast to other reports which indicated a maximal increase in total cholesterol at the thirtieth week of pregnancy,[11] our findings demonstrated a progressive rise throughout pregnancy. The mean increase from the first trimester to labor was slightly over 100 per cent as compared with reported values of 10 to 100 per cent.[11, 13] In agreement with the findings of Popper and Schaffner,[12] hypercholesterolemia was common in the latter stages of pregnancy, 51 of 69 women in labor having values in excess of the upper limit of normal range (300 mg. per cent).

The possibility that the maternal increase might be due to elevated fetal total cholesterol was not borne out, inasmuch as the fetal mean value is 228 mg. per cent *lower* than that of the corresponding maternal value. It has previously been suggested that the maternal elevation is not true to an impairment of cholesterol excretion since sterol balance is negative in pregnancy.

A current theory of the physiology of the adrenocortical stimulating hormone of the pituitary (ACTH) states that even as the adrenal is stimulated to release and/or manufacture corticosteroids under ACTH influence, so does the liver combine squalene radicals under pituitary control, resulting in cholesterol formation. If, indeed, elevated ACTH levels in pregnant women are the prime factor in the elevated total cholesterol values, this has yet to be demonstrated.

One would anticipate that with a normal liver the extra cholesterol would be esterified in the normal manner. Increased total esterification of an unusually large amount of total cholesterol would be a normal reflection of the homeostatic efforts of the liver during pregnancy. Despite the claim that the ester fraction decreases during pregnancy,[11] present results indicate no significant change in cholesterol esterification during normal pregnancy.

Alkaline phosphatase activity was elevated in both maternal and fetal sera. The maternal rise occurred after the second trimester of pregnancy. In view of the normal maternal bilirubin level, it was probably not due to extrahepatic obstructive factors. It might have been related to increased bone metabolism during pregnancy.

The fall in total protein observed in maternal blood involved both albumin and globulin levels and may be related to plasma dilution factors in part. The return of maternal globulin to normal at labor, however, was independent of the albumin status, which remained lowered. Globulin in fetal blood was significantly lower than in the mother and accounted for the lower fetal total protein relative to maternal total protein. The low globulin level in the fetus was reflected by the relatively low thymol turbidity function of fetal serum. Maternal mean serum thymol turbidity (which was normal) was four times the fetal value.

All maternal samples tested revealed normal total bilirubin values as well as normal direct bilirubin. This is contrary to elevated values described elsewhere.[17, 24] Fetal total and direct bilirubin was elevated, most likely because of an increased rate of blood destruction of the immature fetal red blood cells.

Cephalin flocculation tests were essentially normal in our series. However, our interpretation of abnormality in this particular test was somewhat liberal.

As previously described,[28] there was a fall in serum cholinesterase activity which began in the first trimester and reached a minimal value from the third trimester onward. To some degree this was associated with hematocrit levels, and might have been related to plasma dilution. Even with normal hematocrits, however, the mean cholinesterase values were significantly depressed. Furthermore, depression was not uniform or constant in degree in all women, whereas we may assume that plasma volume increase is present in all pregnancies.

If the depression of serum cholinesterase in pregnancy was purely a function of hemodilution, it should have been relatively constant in all women according to their stage of pregnancy, since plasma volume increases tend to be in standard ranges for each trimester.

Furthermore, a fall due to hemodilution implies that the liver was unable to restore homeostatic balance in cholinesterase metabolism by overproduction of the enzyme in compensation for hemodilution effect. Although the life of the cholinesterase molecule is, like that of the albumin molecule, considered to be about 28 days, and a normal steady rate of hepatic production of the enzyme has been postulated, the rate of production increases to compensate for irreversible destruction of serum cholinesterase by diisopropyl-fluorophosphate (DFP).[31] Also, in states of low serum albumin concentration, it is probable that the liver overproduces both albumin and cholinesterase as in nephrosis.[32] In fact, albumin and serum cholinesterase activity often are related.[33, 34, 35] However, this relationship is general and not necessarily quantitative in nature. For example, in the aforementioned nephrosis, with very low albumin, serum cholinesterase activity is correspondingly high. This is most likely due to continued loss of the much smaller albumin molecule at the glomerular level with cholinesterase retention.[32]

On the other hand, we have been unable to demonstrate in vitro anticholinesterase activity in the serum of pregnant women. This may be a failure, of course, in our testing techniques.

Nutritional factors do influence cholinesterase activity levels. These women were in good nutrition throughout their pregnancies, however. Estrogen is known to be an in vitro anticholinesterase and may exert an influence in vivo as estrogen levels rise during pregnancy, although, in rats, cholinesterase rises in late pregnancy, presumably because of elevated estrogen levels.[36]

To some degree the hematocrit is directly proportional to cholinesterase activity but, even with normal hematocrit ranges, the mean cholinesterase is significantly depressed during pregnancy.

It is our opinion that multiple interrelated factors combine to produce the fall in serum cholinesterase activity seen in normal pregnancy. These include hemodilution, hormone balance, possible specific inhibition of hepatic function, and in vivo anticholinesterase activity.

The possible significance of these findings in obstetrical practice is in both the clinical and research areas. We feel that clearer understanding of liver function in normal pregnancy will be of help in the evaluation of possible hepatic disease occurring during the prenatal state. We have demonstrated that a slight alkaline phosphatase elevation is of no significance in normal pregnancy and that values as high as 10 to 15 Bodansky units may be seen without liver disease. On the other hand, it seems clear that any bilirubin elevation in the

mother during pregnancy must be considered as probably abnormal. It is also of interest that a significant fall in cholesterol esters is not usually seen in normal pregnancy. Elevation of thymol turbidity or cephalin flocculation in the range of 3 to 4 plus in 48 hours is abnormal in pregnancy. Cholinesterase levels in nonpregnant women have been of great value in following the course of hepatic disease. In pregnant women, however, low serum cholinesterase values are normally found. This enzyme test is, therefore, of relatively little value in the study of liver disease during pregnancy.

The aforementioned range of values for certain liver function tests during normal pregnancy having been established, it will now be possible to re-explore the entire problem of the pre-eclamptic and eclamptic patients with special reference to the relationship of cholinesterase metabolism and other liver function tests to the etiology and course of the toxemic state. The entire area of the mechanism of estrogen-cholinesterase interrelationships in humans, with special reference to possible effects on the cholinesterase end-organ muscle of the uterus, also should be studied. With values now available for fetal blood as obtained from placental veins, it will be possible to study the effect of liver disease or toxemia in the mother on the fetal liver function.

Summary

1. Maternal and placental vein sera were studied in a series of prenatal clinic patients with normal pregnancies.

2. Maternal serum cholesterol increased throughout pregnancy to the time of labor. Fetal cholesterol was quite low. Both maternal and fetal cholesterol esterification were normal.

3. Serum alkaline phosphatase was elevated in both mothers and babies.

4. Serum albumin decreased in the mother's serum throughout pregnancy, whereas globulin fell and then rose prior to delivery. Fetal proteins were low. Fetal globulin was lower than fetal albumin.

5. Maternal and fetal thymol turbidity was normal but fetal values were much lower than corresponding maternal values.

6. Cephalin-cholesterol flocculation was essentially normal in mother and baby.

7. Serum bilirubin, total and direct, was normal in mothers, elevated in babies.

8. Serum cholinesterase activity fell during pregnancy and was low in the fetus. Individual maternal values were unrelated to maternal race, fetal sex, fetal weight at birth, or maternal parity.

9. The hematocrit of maternal and fetal blood was determined. It was roughly proportional to serum cholinesterase activity. Within normal hematocrit ranges, however, mean serum cholinesterase activity was significantly depressed during normal pregnancy. This indicates that further explanation is needed to account for the marked fall in serum cholinesterase activity in maternal blood during normal pregnancy.

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THE UTERINE DECIDUA IN ECTOPIC PREGNANCY: ITS NATURAL HISTORY AND SOME BIOLOGIC INTERPRETATIONS

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THE term "decidua" has a dual meaning in gynecic parlance. In its nominal form it denotes the endometrium of pregnancy in species whose placentas are shorn and cast off from their maternal attachment after parturition. In the human and other primates the decidua consists of three strata, readily distinguishable in the early stages of pregnancy as the compacta, the spongiosa, and the basalis. After implantation the gestational endometrium undergoes regional differentiation in relation to the ovum, the zone subjacent to the latter being termed the decidua basalis or serotina, the extraplacental part of the uterine lining as the decidua vera or parietalis, and the layer enveloping the gestation sac as the decidua capsularis.

The word "decidua" also has a more restricted meaning, especially in its adjectival form, identifying the endometrial stroma characteristic of pregnancy. Very early in gestation the connective tissue of the endometrium undergoes a remarkable morphologic and histochemical transformation into larger, polygonal epithelioid cells with spherical, eccentric nuclei and mildly basophilic cytoplasm, supported by a complex reticular matrix. These specialized units are known as decidual cells; the change, as the decidual reaction. All evidence points to its endocrine mediation by progesterone, but not to its absolute specificity for pregnancy. Decidual changes morphologically and histochemically indistinguishable from those normally occurring in early gestation can be produced in nonpregnant animals (guinea pig, rat, dog, monkey) by trauma.[15, 24] In the human, also, the decidual reaction occasionally develops in the absence of pregnancy, reflecting an exaggerated response to the corpus luteum or increased or prolonged stimulation, as from a corpus luteum cyst or hormone-producing neoplasm of the ovary.[33]

The decidual reaction is usually most pronounced alongside the endometrial blood vessels, especially the coiled arterioles. Typical decidual changes may also occur, however, in the myometrium[36] and outside the uterus. Common sites for ectopic decidua include the surface of the ovary, the cervix, and pelvic peritoneal adhesions.[20] Decidua has also been found in such diverse and remote locations as the appendix, spleen, and lymph nodes.[9]

During the first trimester of pregnancy the decidua vera thickens greatly, up to 1 cm. Subsequently, however, the uterine lining thins out, rarely measuring more than 1 to 2 mm. at term. Several possible mechanisms have been mentioned to explain this gradual shrinkage of the decidua. Distention of the uterus is generally regarded as the principal factor. Webster[35] suggested inanition resulting from choking of the lymphatics as an alternate cause. Others have postulated digestion of the decidual cells by the fetal trophoblast. A final possibility, absorption of the decidua by the mother, receives credence from observations on the contradeciduate mole, Talpa, the placenta of which is not shed after birth of the young, but gradually absorbed from the uterus.[2]

Full fruition of the normal decidual reaction entails a striking dissociation of stromal from glandular response to hormone stimulation. Each of these endometrial components reacts initially to the corpus luteum in characteristic fashion, the stroma with its epithelioid change, the glands by increased convolution, serration, and secretion. With continuing pregnancy, however, the endometrial glands fail to maintain their early prominence, being superseded by the decidual stroma. Secretory activity peters out, a phenomenon termed "secretory exhaustion," the glands in the superficial strata being replaced in large measure by the expanding stromal mass.

The histologic appearance of the decidua at various stages of pregnancy has been described by Webster, Broders and McDonald,[5] Sturgis,[32] Rutherford,[26] and others. During the early months the glands dominate the field, reaching the height of their secretory activity at about the eighth week. This activity then gradually wanes, and by the fifth month or sooner not only has this function completely subsided but the glands have lost their papillary infoldings and serration, their lumina have been narrowed as if by encroachment by the surrounding decidual stroma, and the erstwhile columnar cells have regressed to an attenuated layer, sometimes imperceptible. As a result the distinction between glands, lymphatic channels,[28] and venules in the spongy decidua becomes difficult and often impossible.

Round cells permeate the decidual stroma in varying number, with localized concentrations appearing here and there in haphazard arrangement. The significance of this cellular infiltrate remains conjectural, but it appears probable that these cells participate in the focal catabolic phenomena associated with aging of the decidua: necrosis, cellular autolysis, venous thrombosis, and blood extravasation. Degeneration of decidua is further characterized by hyalinization, and vacuolization, with shrinkage of the cells, pyknosis of the nuclei, and loss of the tissue's normal basophilia.

The minute hemorrhages that occur in the decidual stroma in early pregnancy have been regarded by some[12] as a localized form of menstruation, resulting from identical vascular phenomena, namely, constriction of the spiral arterioles followed by reflux venous hemorrhage[27] into the ischemic tissue. Rupture of the extravasated blood into a decidual gland, as has been demonstrated in early human ova,[4] provides a ready explanation for the "placental sign" bleeding in women[30] independent of the erosive action of the trophoblast.

Circumstantial evidence points to the decidua's benefactions to both fetus and mother. Rich in lipids and glycogen, it probably provides nutriment for the young embryo. Interposed between the placenta and the myometrium, it serves also as a buffer, protecting the uterine wall against trophoblastic invasion. After birth of the infant, separation of the placenta occurs by cleavage through the zone of canalized fibrin in the decidua basalis. In the rare cases in which the decidual layer is lacking or deficient, placenta accreta results.

Two centuries ago Boehmer,[3] describing the genitals of a woman who died of an ectopic pregnancy, called attention to the decidual membrane lining the uterus. This observation was confirmed two decades later by John Hunter,[17] who has often been credited, erroneously, with the original discovery of the uterine decidua in ectopic pregnancy. Studied anew many times in the ensuing years, the phenomenon is now well established but varying estimates prevail concerning the frequency with which uterine decidua is recoverable in cases of early tubal pregnancy.[10, 18, 19, 22, 23, 29] Polak and Wolfe found decidua in the uterus as long as the ovum remained alive in the tube. Siddall and Jarvis recovered decidua from each of a small series of patients in whom vaginal bleeding had been of less than 10 days' duration. Moritz and Douglass, on the other hand, reported uterine decidual tissue in only 15 per cent of their cases of tubal pregnancy; and Romney, Hertig, and Reid, in 19 per cent. The absence of decidua in the remainder has been attributed to its prior autolysis or slough, either piecemeal as in menstruation or as an intact decidual cast. The endometrial decidual reaction has also been noted in rare cases of cervical pregnancy.[25, 31]

In common with decidual tissue outside the uterus, the uterine decidua associated with ectopic pregnancy lacks three characteristics of the decidua basalis of intrauterine pregnancy: regions of coagulation necrosis resulting from the sting of the trophoblast; lateral and basal sinuses subjacent to the embedded ovum, forerunners of the intervillous space; and a layer of canalized fibrin (Nitabuch). The significance of this last feature has been stressed particularly by Knepper.[14]

Few ectopic pregnancies progress beyond the early months without recognition and treatment. In the rare cases that advance to a later stage the uterus does not usually become available for histologic study. As a result, the natural history of the uterine decidua allowed to progress to term without the complicating proximity of the trophoblast and fetus has not been recorded. In a conjectural vein Novak and Darner wrote: "It seems safe to assume, although we have no direct evidence bearing on the point, that in . . . tubal pregnancy advancing without interruption to the later months, the uterine decidua would exhibit the same features as the decidua vera of intrauterine pregnancy, with perhaps the absence of such thinning and atrophy as is explained by the mechanical pressure of the amniotic contents."

In species with bicornuate uteri the nonpregnant horn provides an ideal medium for observation of the pregnancy changes in the endometrium unaffected directly by the gestation sac and trophoblast. In the normally uniparous cow and ewe, for example, it has long been known that the empty and

TABLE I. SUMMARY OF CASES

CASE	AGE (YEARS)	GRAVIDITY	PARITY	PREGNANCY SITE	DURATION (WEEKS)	SIZE OF FETUS	CONDITION OF FETUS OR TROPHOBLAST	VAGINAL BLEEDING	DECIDUA (MM.)
1	38	v	iii	Tube	4½	----	Dead	No	9
2	29	i		Tube	8	Sac 4 by 3.5 by 2.5 cm.	Live	Yes	5.4
3	34	viii	ii	Tube	8	----	Dead	Yes	--
4	37	ix	vi	Cervix	9	2 cm.	Live	Yes	2.2
5	31	ii	i	Tube	10	3.5 cm., crown-rump	Live	Yes	14
6	37	iv	0	Tube	11	----	Live	Yes	6
7	36	iii	ii	Tube	12	8.3 cm.	Live	Yes	3.6
8	37	vii	0	Tube	12	----	Dead	Yes	--
9	34	iv	ii	Tube	20	320 grams	Dead	No	6.2
10	38	ii	0	Abdomen	32	1,450 grams	Live	Yes	2.7
11	33	i		Abdomen	38	3,265 grams	Live	Yes	5.3
12	30	i		Tube	Term	3,400 grams	Live	Yes	3.5

gravid horns of the uterus undergo different changes. This difference has been recorded in more detail in several other species. In the unilaterally pregnant rat, studied with great care by Allen,[1] the glandular hyperplasia of early pregnancy retrogresses during the later stages and the stroma becomes edematous; and after the seventh day the endometrium is no longer capable of responding to mechanical (needle prick) stimulation by deciduoma formation.

Courrier and Kehl[6] and others[7, 13] performed unilateral salpingectomy in rabbits and recorded the changes in the empty horn during subsequent pregnancies. In this species the progestational condition of the sterile horn persists until the sixteenth day, or midterm. Within the next few days degenerative changes set in. The stroma becomes more compact, the glands begin to shrink, and the epithelium sloughs into the lumina. Necrosis without hemorrhage continues to the twenty-eighth day, when the regenerative process begins in preparation for the next estrus. Still different changes occur in the mouse uterus. During the second half of pregnancy in this species, according to Deanesly and Parkes, the sterile horn undergoes a fresh phase of development, consisting of an increase in number and dilatation of the glands sufficient partially to obstruct the uterine lumen in places. About 4 days before term blood extravasates into the stroma, as in the menstrual primate endometrium. In the sterile horn of the guinea pig uterus the same authors observed no morphologic modifications beyond the slight changes that normally occur during pseudopregnancy. The alterations in the nonpregnant horn of the unilaterally gravid cat uterus have been described by Gros.[11] The superficial fringes of the lacelike endometrium remain intact to about the fortieth day (23 days before term), although the glands become less prominent in the deeper layers. Soon thereafter leukocytic infiltration begins and the epithelium desquamates, but regression to the nonpregnant condition is not completed until after parturition.

The bicornuate Tasmanian rat kangaroo normally liberates only one ovum at ovulation, successive pregnancies alternating between the two horns of the uterus. During the first half of gestation, which lasts about 6 weeks in this species, both horns undergo identical changes.[8] At midpregnancy, however, the nonpregnant horn shrinks slightly, and during the ensuing period glandular secretion diminishes, much of the epithelium is lost, and the stroma becomes edematous. Just before parturition the interstitial fluid in the pseudopregnant mucosa is rapidly extruded into the glandular lumina and out of the uterus by vigorous contractions of the myometrium.

In the uniparous giant fruit bat *(Pteropus giganteus)* implantation of the fertilized ovum is restricted to a small region just below the uterotubal junction in either uterine horn. The endometrium in this narrowly circumscribed area becomes markedly swollen and undergoes the characteristic changes of pregnancy, while the remainder of the endometrium, in both the pregnant and nonpregnant horns, remains relatively inactive throughout gestation, virtually unaffected by the corpus luteum.[16] van der Horst and Gillman[34] have described an almost identical phenomenon in the elephant shrew (Elephantulus).

Present Observations

The fate of the human decidua, freed of the local effects of the conceptus, can be studied in uteri excised, without preliminary curettage, from patients at various stages of ectopic pregnancy. The present material includes 12 such specimens, associated with ectopic pregnancies of 4½ weeks to full term. The cardinal data from these cases are summarized in Table I.

CASE 1.—Unit No. 839463. Tubal pregnancy, 4½ weeks. This 38-year-old Negro woman had previously had 3 normal term pregnancies and a left tubal gestation, which was terminated by salpingectomy in 1951. Her last menstrual period began March 20, 1953. On April 21 she collapsed with a sudden attack of severe pain in the lower abdomen and underwent operation for a ruptured right tubal pregnancy. The uterus was removed, together with the right tube and ovary. The endometrial cavity was lined with a luxuriant decidua, which measured up to 9 mm. in fixed section. The glands of the spongiosa showed a well-marked gestational pattern, but their secretory function appeared largely exhausted (Fig. 1). Broad bands and delicate strands of decidual stroma, undergoing autolysis and heavily infiltrated with lymphocytes and polymorphonuclear leukocytes, separated the exhausted glands and dilated vascular channels of the superficial half of the endometrium. The compacta contained areas of interstitial hemorrhage and superficial slough. Sections of the tube (Fig. 2) showed sheets of trophoblast and young chorionic villi with stromal edema and beginning hyalinization, and in places loss of their epithelial covering, indicating earlier death of the ovum.

CASE 2.—Unit No. 863169. Tubal pregnancy, 8 weeks. This 29-year-old nullipara with known fibroids menstruated last on Jan. 28, 1947. On March 13 she noticed scant vaginal bleeding and 2 weeks later complained of severe abdominal pain. The myomatous uterus extended to 6 cm. below the umbilicus. The blood hemoglobin concentration was 5.4 Gm. per 100 c.c. Operation on March 28, 1947, revealed fresh bleeding from a ruptured left tubal pregnancy. The affected tube and the myomatous uterus were excised together. The intact fetal sac measured 4 by 3.5 by 2.5 cm. The uterus was lined with a decidual membrane up to 5.4 mm. thick in histologic section. Its superficial layers consisted of transformed stromal cells in almost solid masses, perforated occasionally by narrow glands lined with low cuboidal epithelium. Secretion persisted in a few of the deeper glands, but most appeared exhausted (Fig. 3). The sectioned placenta showed sheets of trophoblast and normal, well-preserved, early chorionic villi with intact Langhans and syncytial layers (Fig. 4).

CASE 3.—Unit No. 970064. Tubal pregnancy, 8 weeks. The patient, a 34-year-old Negro woman, gravida viii, para ii, had her last normal menstrual period around the end of July, 1949. On August 31 she had an atypical, heavy flow, accompanied by the passage of pieces of tissue (probably decidua). She complained of intermittent abdominal pain throughout September, and bleeding recurred on the fourteenth of the month. Operation on September 28 revealed a fibroid uterus and a left tubal pregnancy that had been ruptured for some time, as evidenced by organized blood clots and adhesions. The excised uterus was lined with an early progestational endometrium devoid of pregnancy changes (Fig. 5). The tubal wall contained chorionic villi in varying stages of demise. Although Langhans and syncytial layers were still distinguishable on some villi, others lacked both; most of the villi showed hydropic degeneration and some, beginning hyalinization (Fig. 6). Contrast with Case 2, a pregnancy of similar duration, and Figs. 3 and 4.

CASE 4.—Unit No. 1267439. Cervical pregnancy, 9 weeks. The patient, aged 37 years, had had 8 previous pregnancies, including 6 full-term and 2 that terminated in spontaneous abortion. The amenorrhea that followed her last normal menstrual period, beginning Jan. 20, 1957, was punctuated by recurrent staining until March 18, 1957, when a profuse vaginal hemorrhage occurred. Cervical pregnancy was correctly diagnosed and complete

Fig. 1.

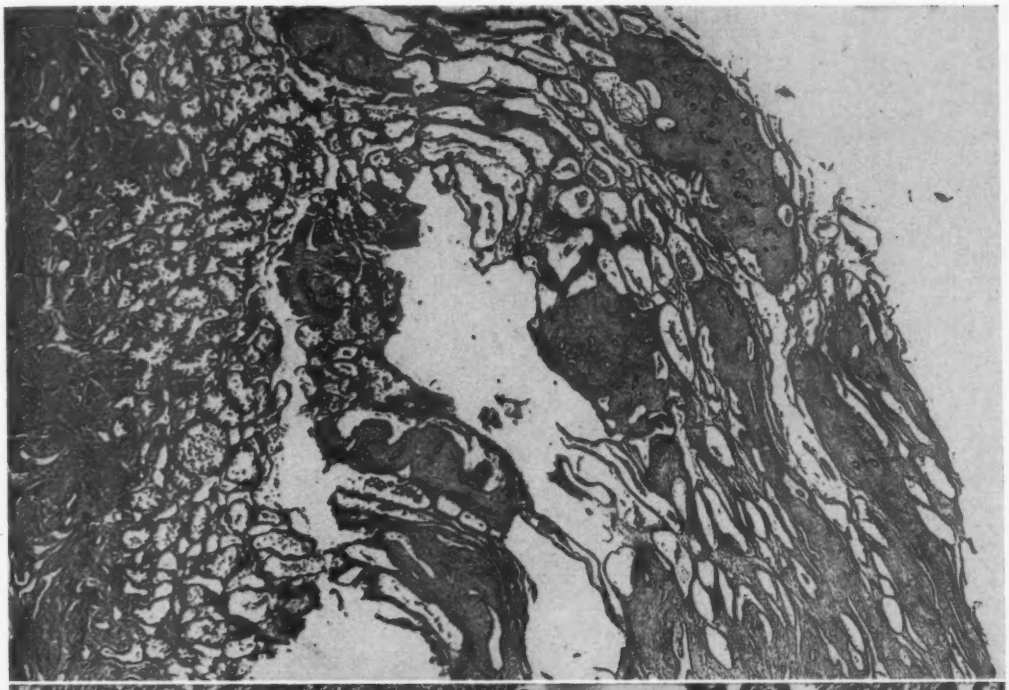


Fig. 2.

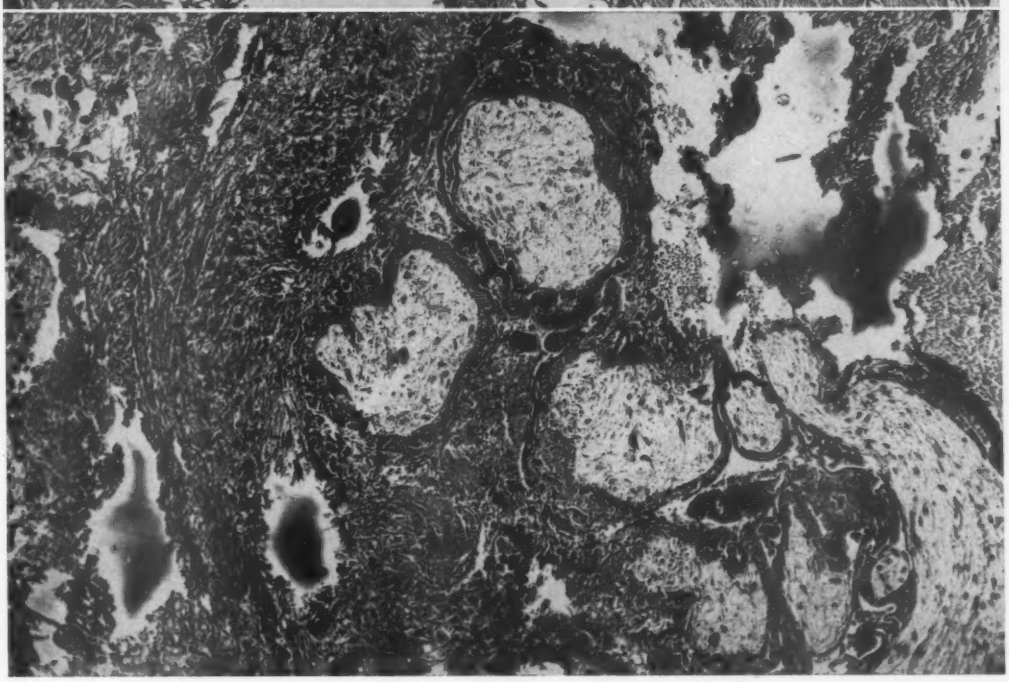


Fig. 1.—Case 1 (tubal pregnancy, 4½ weeks). Section of uterus. Decidua shows early degenerative changes. (Central defects in section are artifacts.)

Fig. 2.—Case 1. Section of tube, showing dead chorionic villi. (Identical magnification used for chorionic villi in all cases.)

Fig. 3.

Fig. 4.

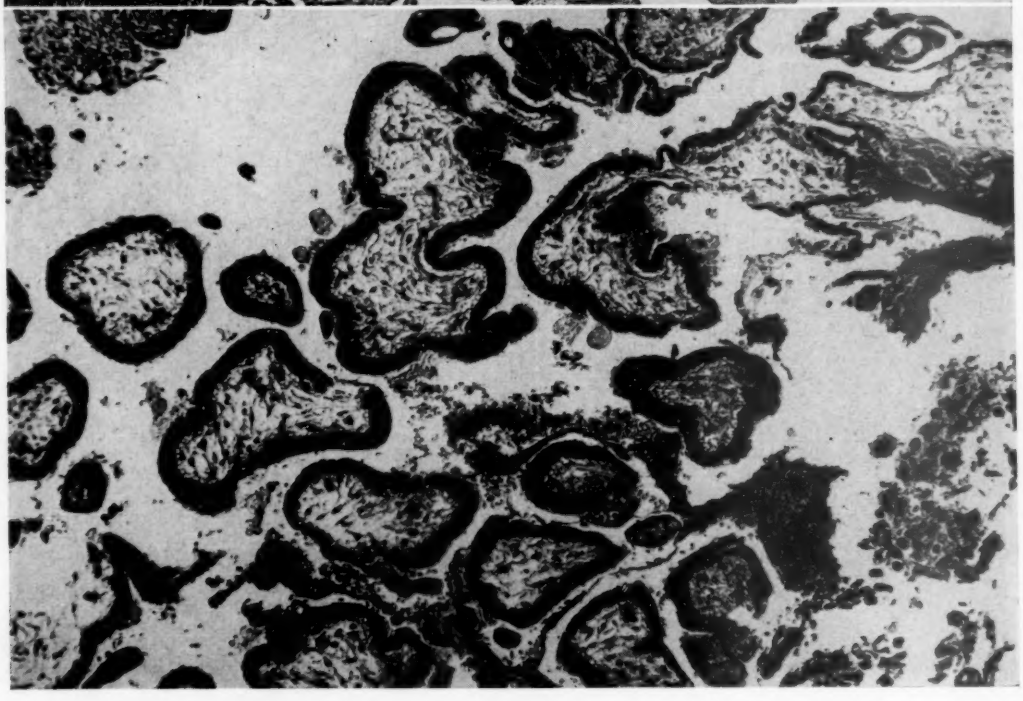


Fig. 3.—Case 2 (tubal pregnancy, 8 weeks). Section of uterus, showing well-preserved decidua.

Fig. 4.—Case 2. Viable chorionic villi in tube wall.

Fig. 5.

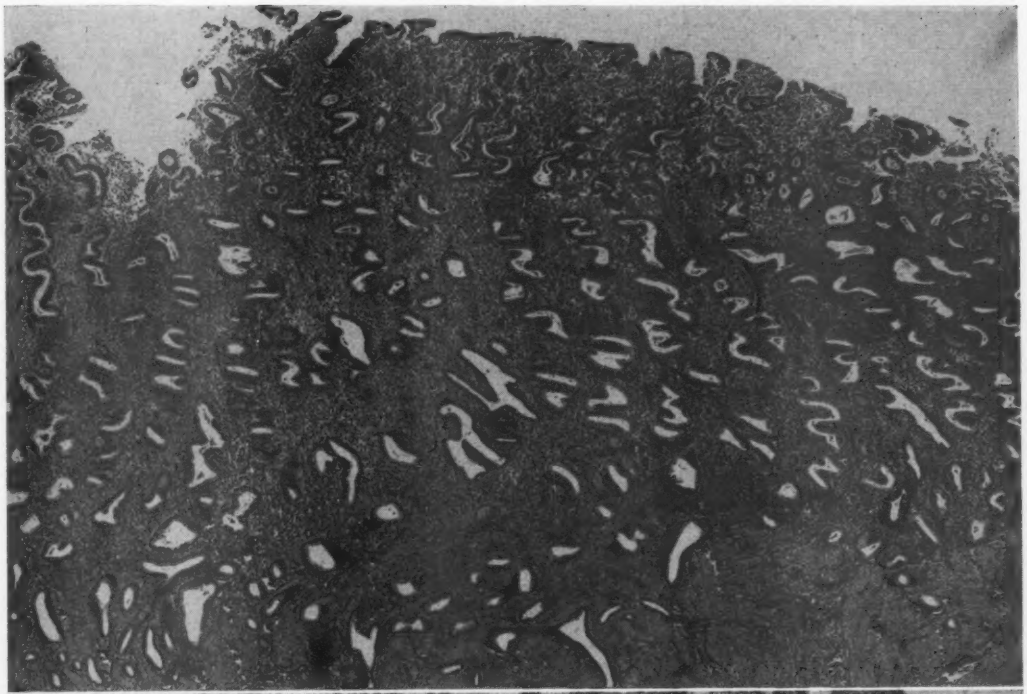


Fig. 6.

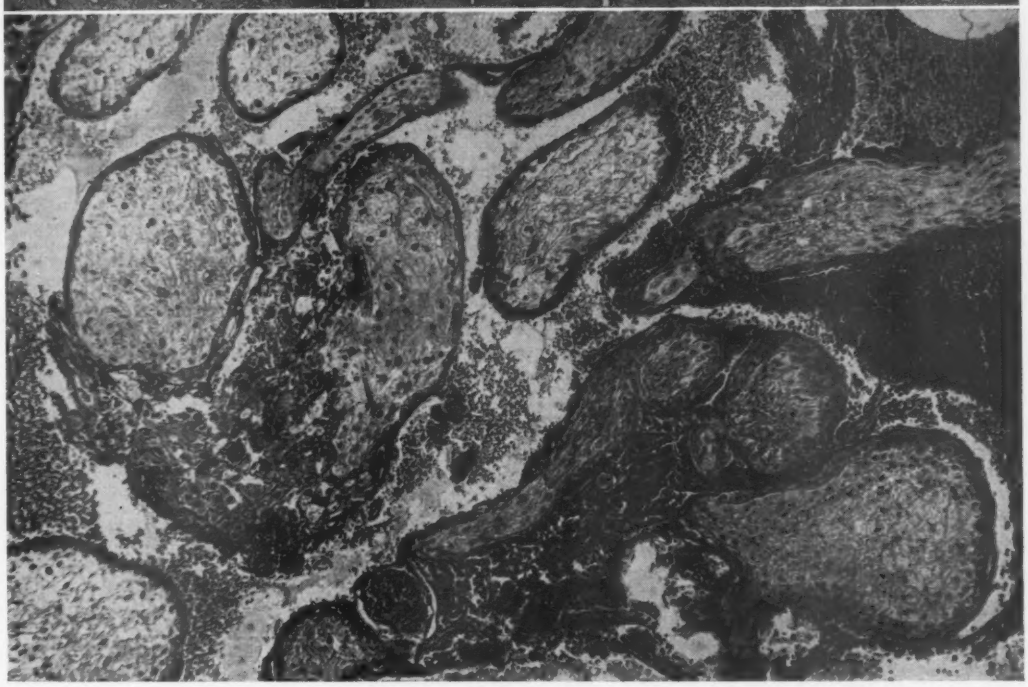


Fig. 5.—Case 3 (tubal pregnancy, 8 weeks). Section of uterus, showing absence of gestational changes in endometrium. Contrast with Fig. 3.

Fig. 6.—Case 3. Section of tube, showing intervillous thrombosis and degeneration of villi. Contrast with Fig. 4.

Fig 7.

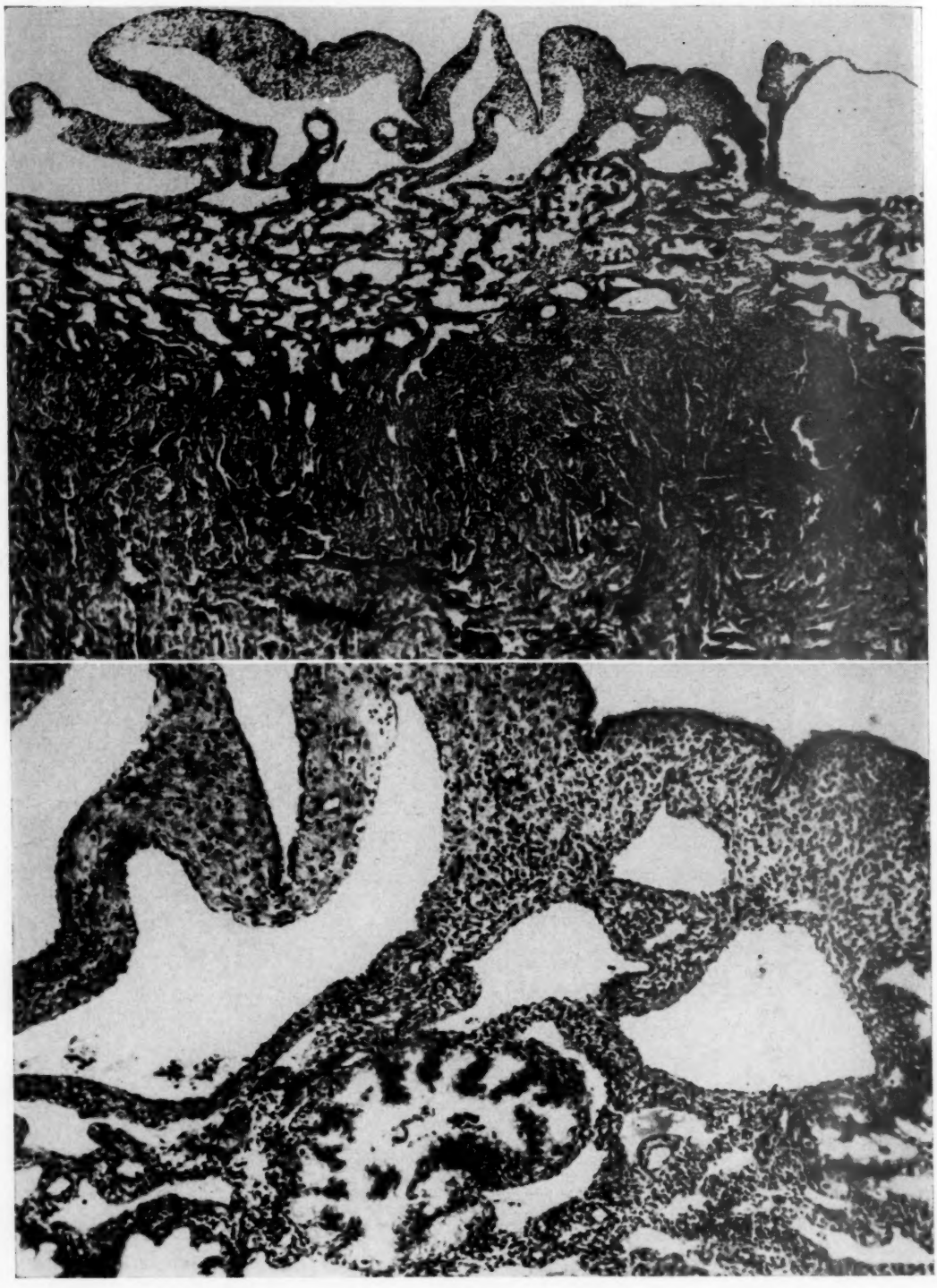


Fig. 8.

Fig. 7.—Case 4 (cervical pregnancy, 9 weeks). Section of uterine corpus, showing extraplacental decidua.

Fig. 8.—Same as Fig. 7, higher power. Note decidual reaction in compacta, and sharp contrast between vascular sinusoids and endometrial glands.

abdominal hysterectomy carried out. The placental site was confined to the cervix. The enucleated gestation sac contained an intact fetus 2 cm. long. The empty uterine cavity was lined with an intact decidual membrane, the surface of which was markedly convoluted (Fig. 7). In histologic section the endometrium measured up to 2.2 mm. in thickness. The stratum spongiosum showed persistent secretory changes, with tufting and serration of the glands, but no apparent communication between the latter and the endometrial cavity. Superficial to the endometrial glands and in sharp contrast to them, markedly dilated, thin-walled veins, empty for the most part, gave the stratum compactum a honeycombed appearance (Fig. 8). The moderately edematous stroma, infiltrated with round cells, showed the decidual reaction characteristic of early pregnancy, most pronounced in the superficial layer. Histologic sections of the placenta showed normal villous structure, with intact epithelium and functional fetal capillaries (Fig. 9).

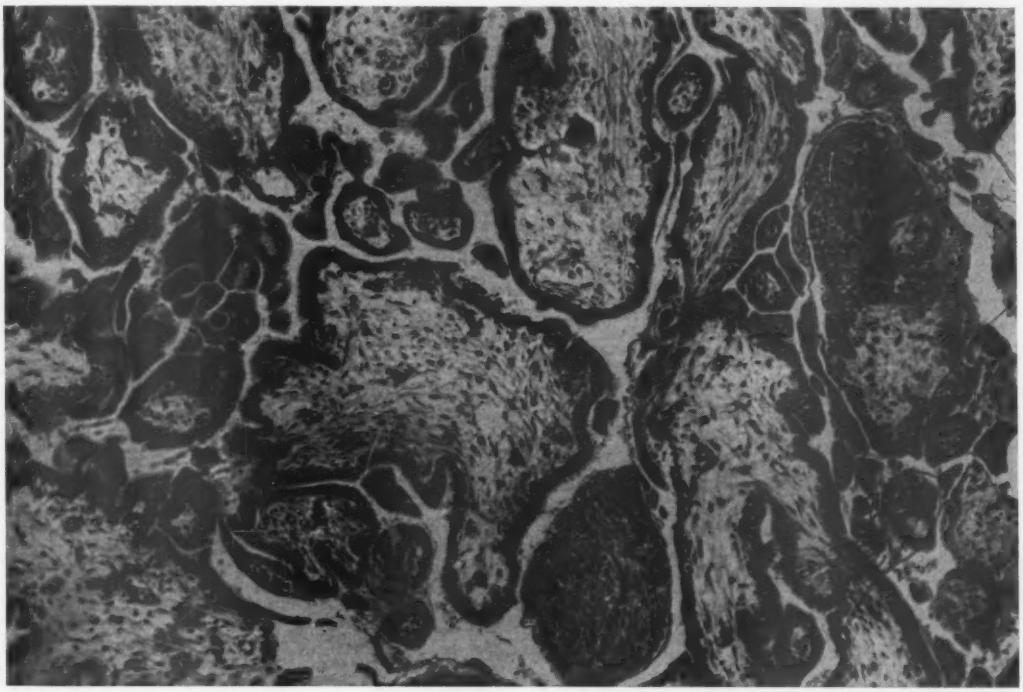


Fig. 9.—Case 4. Section of cervical placenta, showing healthy chorionic villi and sheets of trophoblast.

CASE 5.—Unit No. 882519. Tubal pregnancy, 10 weeks. The patient, a 31-year-old Negro secundigravida, last menstruated on Aug. 25, 1947. Slight vaginal bleeding occurred near the end of September and again in early October; in mid-October she complained of abdominal cramps. The Friedman test was positive on October 13. Increasing pain led to the diagnosis of ectopic pregnancy, for which operation was performed on November 3. The ruptured left tube, an intact fetus of 3.5 cm. crown-rump length, a small, fragmented placenta, and the myomatous uterus were removed. The uterus contained a decidual lining 1.4 cm. thick in histologic section. Most of the glands of the spongiosa still showed some secretory activity. Many, however, had regressed to an inactive state and were lined with cuboidal epithelium. A smaller number of round and irregular glands, lined with flattened epithelium, lay embedded in the thick layer of compacta, which was made up chiefly of a well-vascularized, healthy-appearing decidual stroma (Fig. 10). Sections of the placenta showed normal young chorionic villi with buds and sheets of trophoblast (Fig. 11).

Fig. 10.

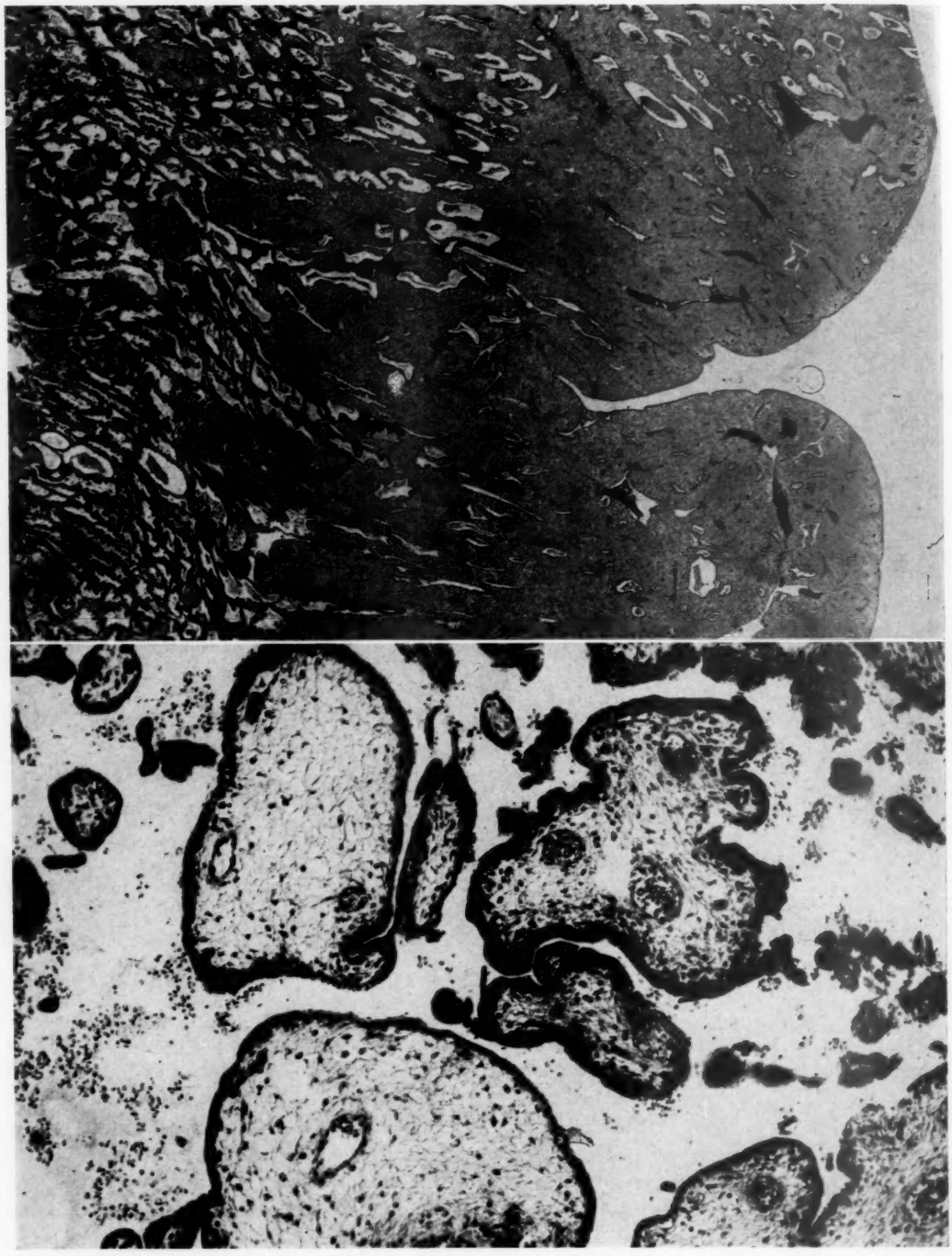
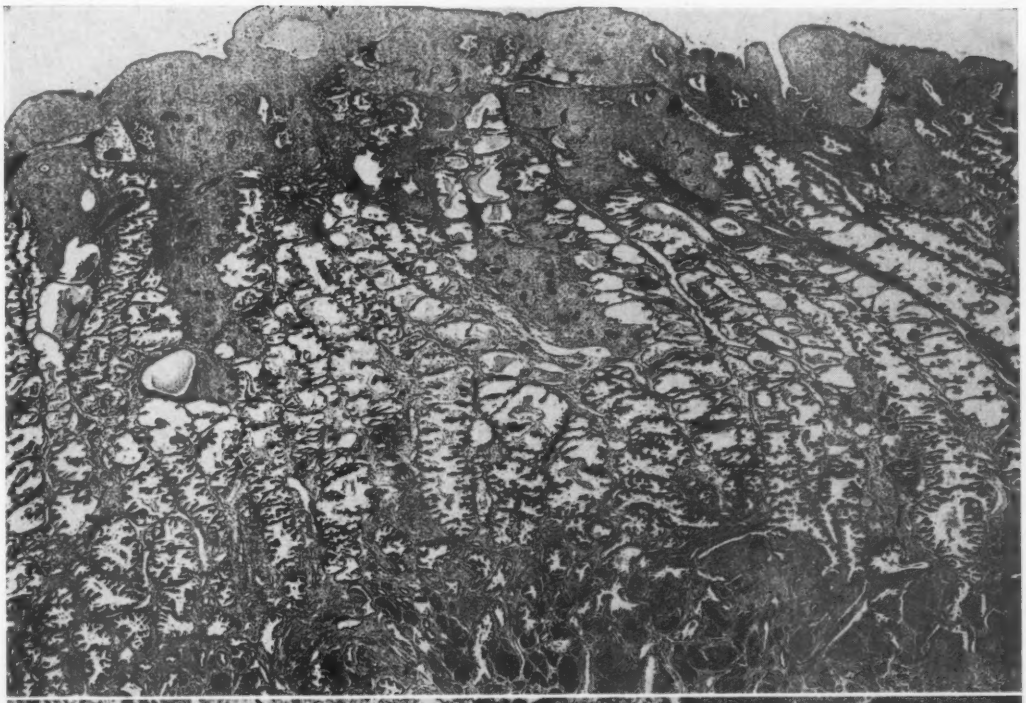


Fig. 11.

Fig. 10.—Case 5 (tubal pregnancy, 10 weeks). Section of uterus, showing intact decidua. Most of the glands have undergone secretory exhaustion.

Fig. 11.—Case 5. Healthy, well-vascularized chorionic villi in tube wall.

Fig. 12.



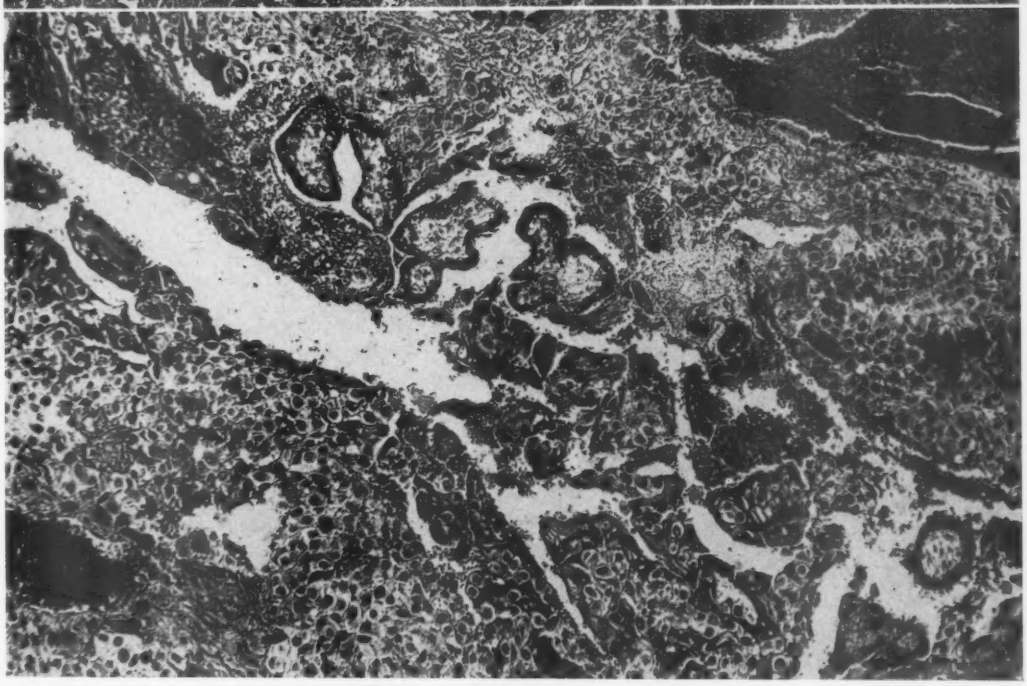


Fig. 13.

Fig. 12.—Case 6 (tubal pregnancy, 11 weeks). Section of uterus, showing intact decidua.
Fig. 13.—Case 6. Section of tube, showing chorionic villi and sheets of viable trophoblast.

Fig. 14.

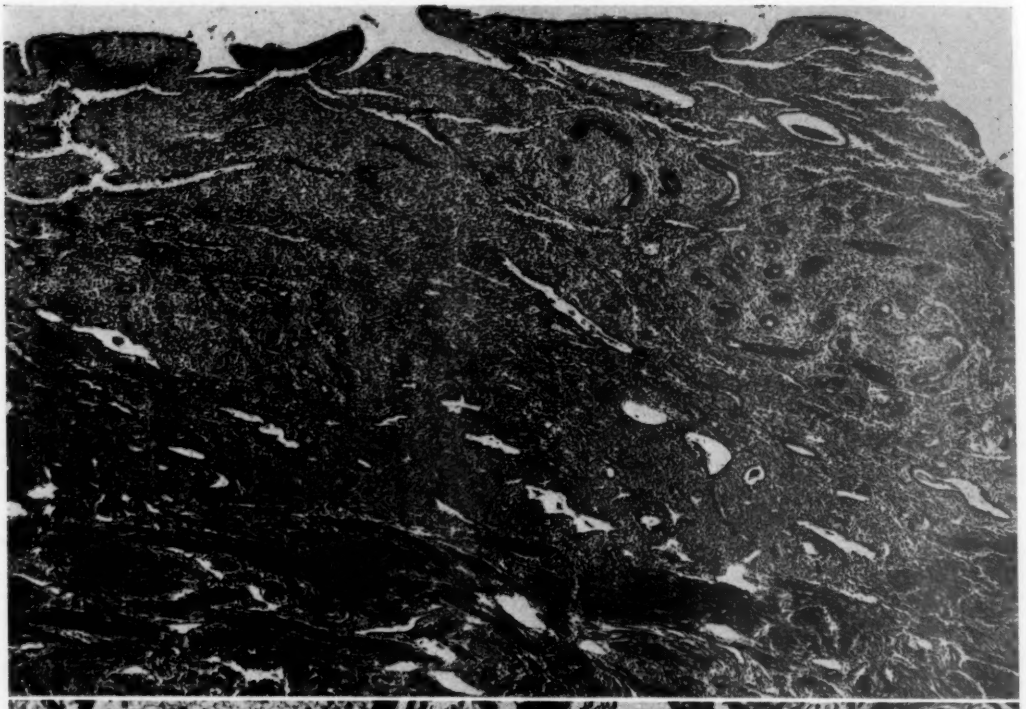


Fig. 15.

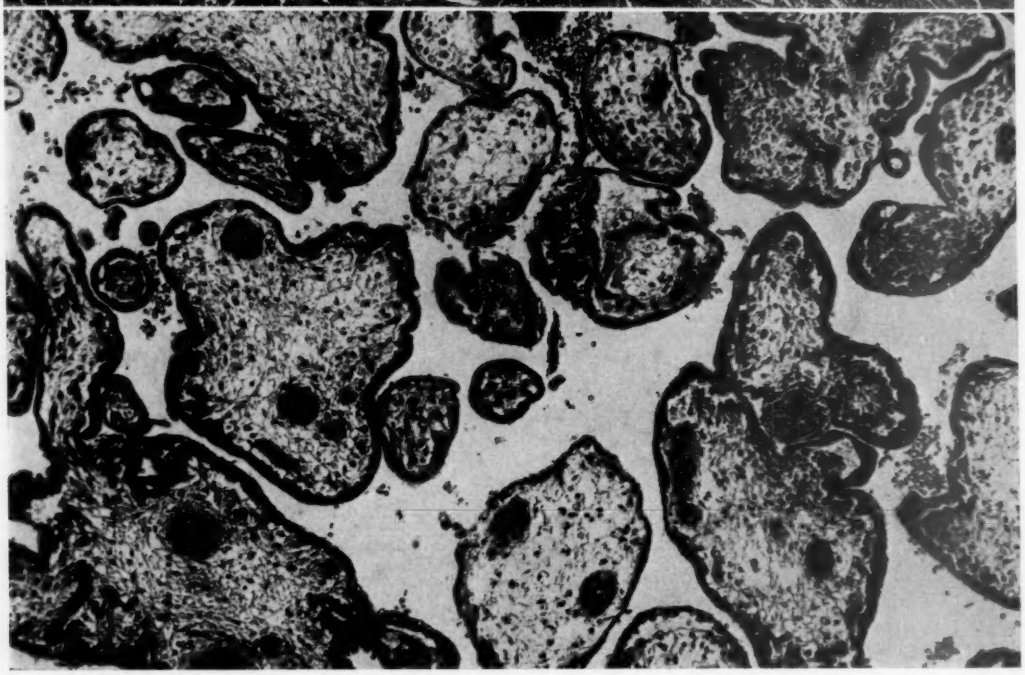


Fig. 14.—Case 7 (tubal pregnancy, 12 weeks). Section of uterus, showing intact decidua. Glands are exhausted. Note spiral arteriole on right.

Fig. 15.—Case 7. Viable chorionic villi in wall of tube.

Fig. 16.

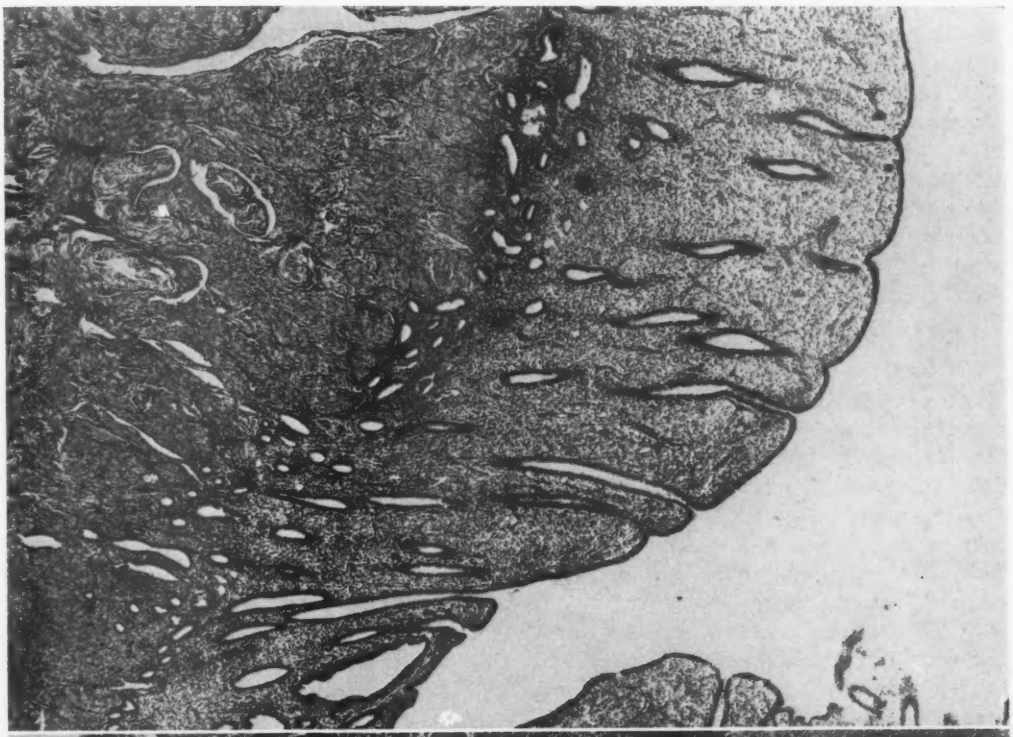


Fig. 17.

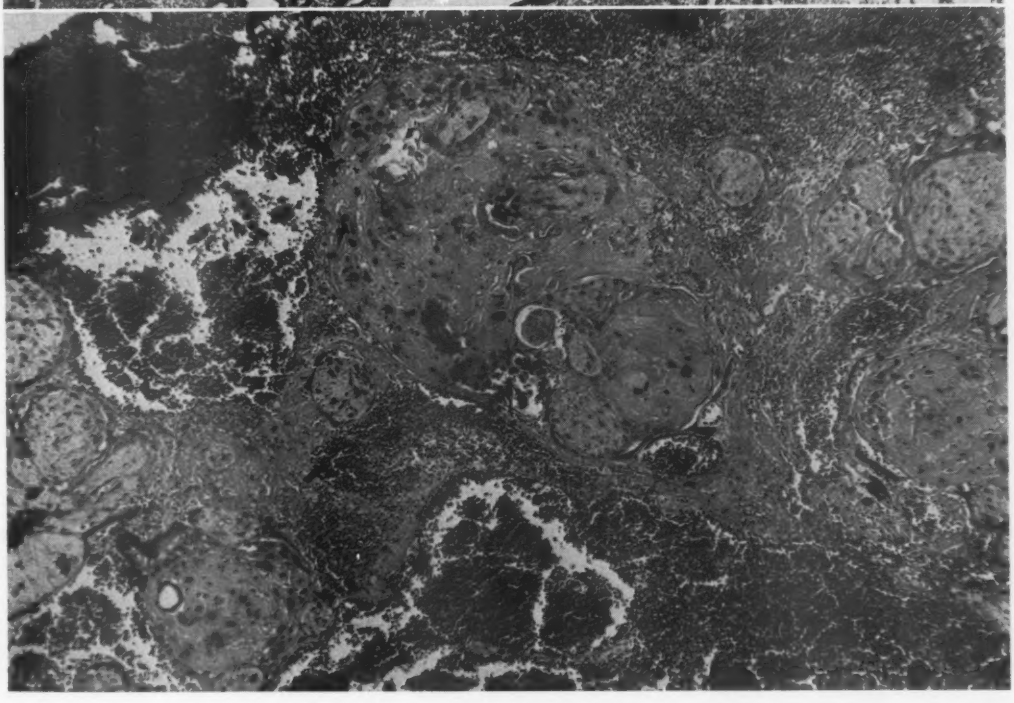


Fig. 16.—Case 8 (tubal pregnancy, 12 weeks). Section of uterus, showing absence of gestational changes in endometrium. (Contrast with Fig. 14.)

Fig. 17.—Case 8. Section of tube, showing hyalinized chorionic villi. (Contrast with Fig. 15.)

CASE 6.—Unit No. 652994. Tubal pregnancy, 11 weeks. This 37-year-old Negro woman had had 3 previous spontaneous abortions, no viable pregnancies. Her last menstrual period began Nov. 1, 1946. She noticed slight bleeding on December 8 and again in January, 1947, when she also complained of abdominal cramps. Severe pain on February 2 led to operation, at which fresh bleeding from a left tubal pregnancy was still in progress. Because of fibroids the uterus was removed with the tube. The uterine decidua measured up to 6 mm. in thickness in fixed section. The spongiosa presented an exceedingly delicate, lacelike appearance, with very thin stromal septa separating the tufted glands. Most of the latter contained inspissated secretion, but the glandular epithelium was mostly exhausted, very few cells showing current secretory activity. The spongiosa was covered with a thick mantle of well-preserved decidual stroma, which encased a few inactive glands and many prominent venous channels (Fig. 12). The wall of the tube contained broad sheets of proliferating trophoblast and a few chorionic villi (Fig. 13).

CASE 7.—Unit No. 895896. Tubal pregnancy, 12 weeks. This patient was a 36-year-old Negro gravida iii, para ii. Her last menstrual period began Oct. 15, 1948. Vaginal spotting was observed on November 15 and for the ensuing 2 weeks. Abdominal pain occurred Jan. 9, 1949, and subtotal hysterectomy and right salpingo-oophorectomy were carried out the following day. The tube contained an intact gestation sac, in which lay a male fetus of 8.3 cm. crown-heel length, attached by a 10 cm. umbilical cord to the placental region of the tubal wall. Sections of the uterus showed an intact decidual lining up to 3.6 mm. in thickness. Exhausted gestational glands of varying size and shape were seen at all levels of the endometrium, the more superficial being lined with flattened epithelium, the more basal with cells still showing a trace of secretory activity. The decidual stroma was well preserved but contained a moderately heavy infiltrate of round cells, with focal concentrations containing polymorphonuclear leukocytes as well (Fig. 14). Sections of the placenta showed normal young chorionic villi covered with Langhans and syncytial layers and containing well-developed, intact fetal capillaries (Fig. 15).

CASE 8.—Unit No. 995136. Tubal pregnancy, 12 weeks. This 37-year-old Negro woman had had 6 prior abortions, including a tubal gestation in 1954, but no viable pregnancies. Her last menstrual period began Jan. 20, 1957. On March 25 a heavy flow occurred, accompanied by the passage of a mass of tissue. The patient then consulted a physician, who made a diagnosis of complete abortion. Vaginal spotting continued, however, and on April 12 the patient experienced severe abdominal pain. Examination disclosed a ruptured ectopic pregnancy, which was treated by right salpingectomy and hysterectomy. The uterus was lined with proliferative endometrium showing no gestational reaction (Fig. 16). The tube contained a hemorrhagic mass measuring 4 by 3 by 3 cm., sections of which showed hyalinized, avascular chorionic villi with atrophy of the covering epithelium and no trophoblastic activity (Fig. 17). Contrast with Case 7, a pregnancy of similar duration, and Figs. 14 and 15.

CASE 9.—Unit No. 038367. Tubal pregnancy, 20 weeks. The patient, a 34-year-old Negro woman, had had 3 previous pregnancies, including an ectopic gestation in the left tube treated by salpingectomy in January, 1953. Her last menstrual period began March 27, 1953. She complained of pain in the right lower quadrant of the abdomen but noticed no vaginal bleeding. A pelvic mass was palpable and roentgenogram revealed a fetal skeleton corresponding to a gestational age of 4½ to 5 months. At laparotomy on Sept. 5, 1953, an intact gestation sac containing a macerated fetus weighing 320 grams was found in the remaining tube. The uterus was removed together with the tube. Extensive organizing hemorrhage was present in the placenta. The uterine cavity was lined by grossly intact decidua measuring up to 6.2 mm. in thickness, but in histologic section necrosis and beginning dissolution of the superficial layer were apparent (Fig. 18). The glands, confined largely to the basal zone, showed minimal secretory activity. The more superficial endometrial strata contained large, tortuous vascular channels surrounded by a partially preserved decidual matrix. The

Fig. 18.

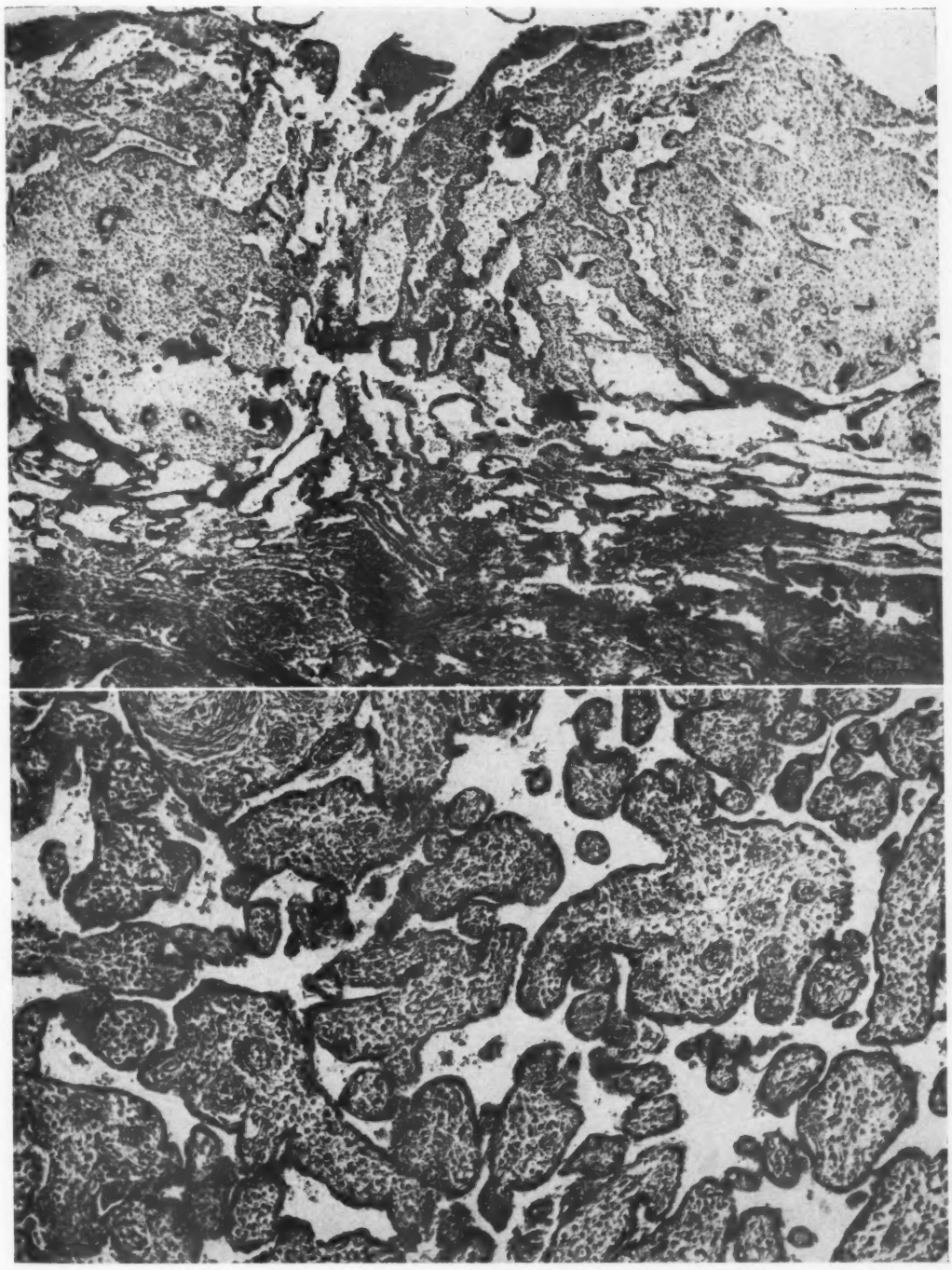


Fig. 19.

Fig. 18.—Case 9 (tubal pregnancy, 20 weeks). Section of uterus, showing beginning necrosis and slough of decidua. Note masses of decidual stroma surrounding spiral arterioles.

Fig. 19.—Case 9. Section of placenta, showing obliterative endarteritis of fetal vessels.

Fig. 20.

Fig. 21.

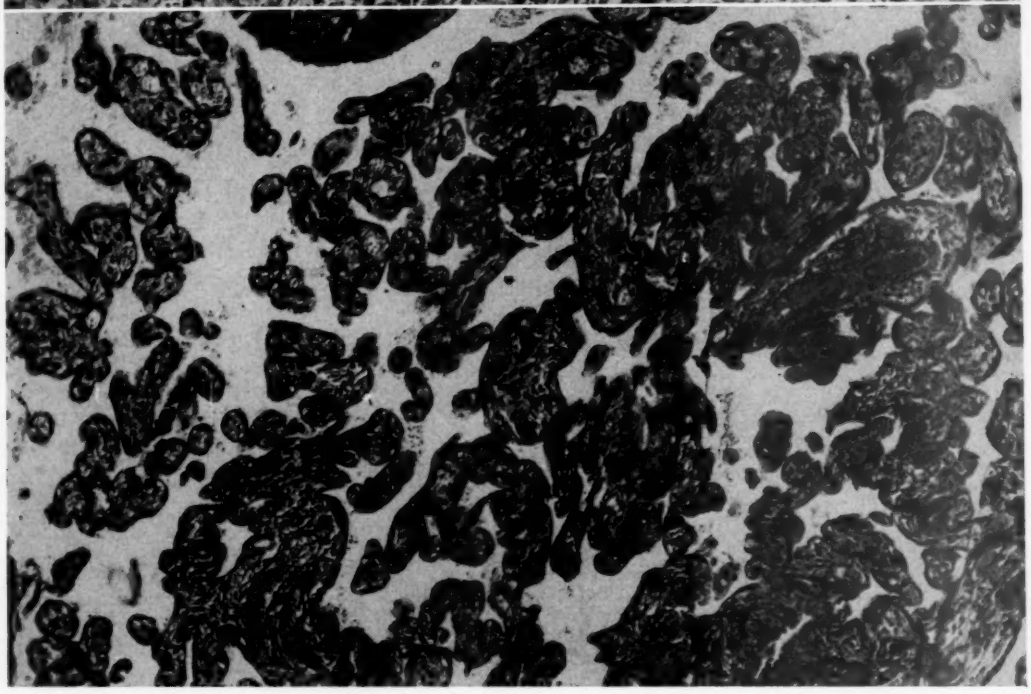


Fig. 20.—Case 10 (abdominal pregnancy, 32 weeks). Section of uterine lining, showing well-preserved decidual tissue. branching vascular sinusoids, and atrophic glands.

Fig. 21.—Case 10. Section of placenta, showing normal chorionic villi.

Fig. 22.

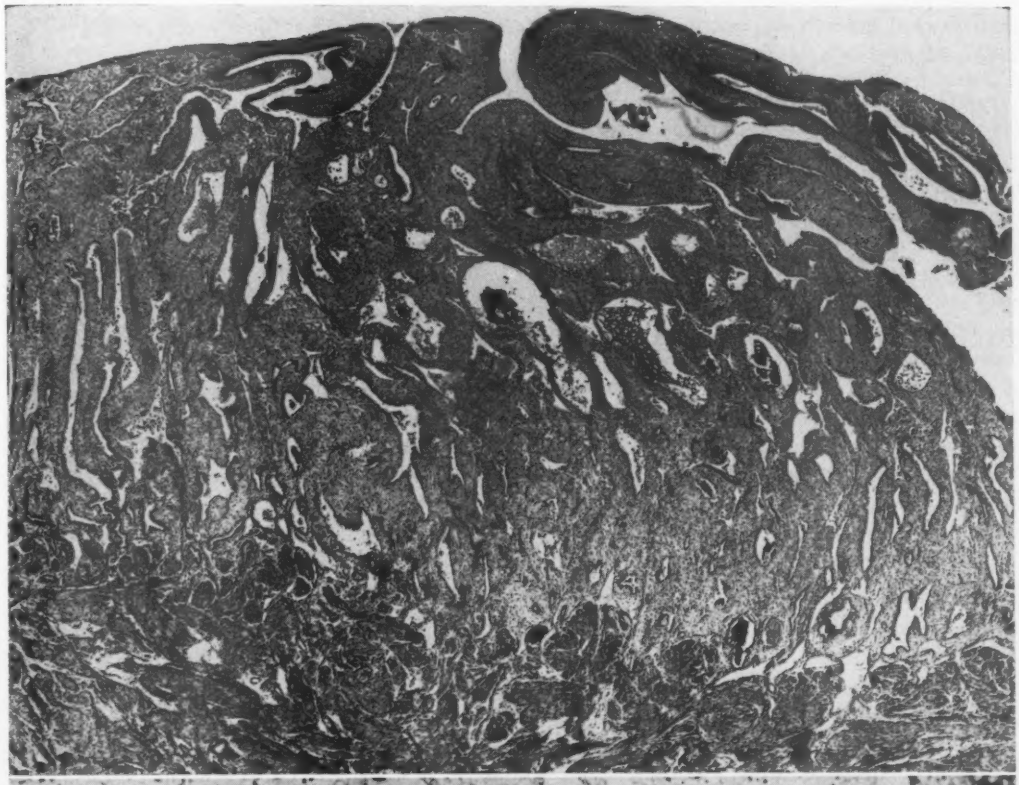


Fig. 23.

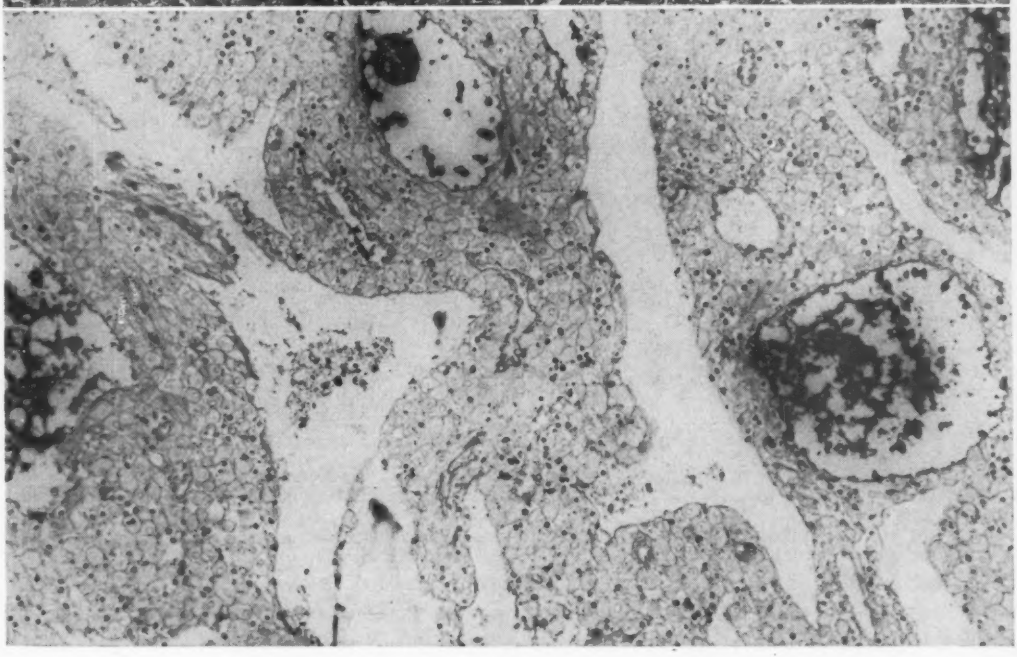


Fig. 22.—Case 11 (abdominal pregnancy, 38 weeks). Section of uterus, showing intact decidua. Glands are atrophic.

Fig. 23.—Same as Fig. 22, higher power (periodic acid-Schiff reaction). Mucin-containing glands contrast sharply with empty vascular channels.

decidual reaction was particularly prominent around the spiral arterioles, which in section appeared embedded in broad sheets of decidual stroma. In sections of the tube the chorionic villi showed mild hydropic changes in the stroma, intervillous fibrin deposition, and obliterative endarteritis of the fetal vessels (Fig. 19).

CASE 10.—Unit No. 037452. Abdominal pregnancy, 32 weeks. This patient was a 38-year-old Negro woman, pregnant for the second time, her first gestation having terminated in spontaneous abortion. Her last menstrual period began March 7, 1955. Slight vaginal bleeding occurred the following month, and on June 28 the patient experienced the first of several attacks of abdominal pain. Because of sudden intraperitoneal hemorrhage, laparotomy was performed on October 23, when an abdominal pregnancy was found. The placenta was attached to the omentum and the serosal surface of the uterine fundus. The fetus, still alive, weighed 1,450 grams. Subtotal hysterectomy and partial omentectomy were carried out, with the placenta still attached to the excised organs. The uterine cavity was lined with decidua which in fixed section measured up to 2.7 mm. in thickness. On microscopic examination only a few endometrial glands could be identified; and these, having undergone complete secretory exhaustion and shrinkage of their lining epithelium, were distinguishable only with difficulty from the more numerous vascular channels, the tortuous and branching endometrial sinusoids. The latter formed a labyrinthine pattern against a background of well-preserved decidual cells, moderately infiltrated with round cells (Fig. 20). The placenta was histologically normal (Fig. 21).

Fig. 24.—Case 12 (tubal pregnancy, full term). Section of uterus, showing necrosis and dissolution of decidua, interstitial hemorrhage, and thrombosis of venous sinusoids.

CASE 11.—Unit No. 192460. Abdominal pregnancy, 38 weeks. This patient, a 33-year-old Negro primigravida, had her last normal menstrual period on Feb. 20, 1954, but bled again lightly on March 20 and 21 and spotted on July 30. Abdominal pain, of which she complained on July 23, was attributed to a degenerating uterine fibroid. Because of a previous myomectomy it was planned to deliver the patient by cesarean section approximately 2

weeks before term, the pregnancy being dated from the March flow. Operation was accordingly undertaken Dec. 14, 1954, when an abdominal pregnancy was encountered and a living male infant extracted, who weighed 3,265 grams. The myomatous uterus was removed at the same time. The endometrial cavity was lined with intact decidua, the maximal thickness of which in fixed section measured 5.3 mm. (Fig. 22). The decidual cells, each surrounded by a delicate reticular membrane, appeared in an excellent state of preservation and contained only a light infiltrate of round cells. Endometrial glands, mostly atrophic, were easily identifiable in the basalis, from which a few could be seen extending up through the decidual stroma; but in the more superficial levels of the decidua the flattened condition of the epithelium made it difficult or even impossible at times to distinguish in hematoxylin and eosin sections between the glands, on the one hand, and the venous sinusoids and lymphatics, on the other. This differentiation was facilitated by special staining reactions, especially the periodic acid-Schiff, which helped identify the basement membrane of the glands and the intraglandular mucin (Fig. 23). Most of the vascular channels appeared empty. The placenta appeared normal in histologic section.

CASE 12.—Unit No. 891793. Tubal pregnancy, full term (previously reported in greater detail by C. P. O'Connell[21]). The patient, a 30-year-old primigravid Negro woman, menstruated last on April 26, 1949. After several antepartum admissions to the hospital because of abdominal pain, urinary tract infection, partial intestinal obstruction, and vaginal bleeding, she underwent laparotomy on Jan. 27, 1950, when a living male infant weighing 3,400 grams was extracted from the right Fallopian tube. Subtotal hysterectomy was carried out at the same time. The uterine cavity was lined with a hemorrhagic and partially necrotic decidual membrane, which measured up to 3.5 mm. thick in fixed section (Fig. 24). The endometrial glands, sparse, compressed by the decidual stroma, and limited largely to the basal zone, were lined with flat or low cuboidal and inactive-appearing epithelium. The cytoplasm of the decidual cells in the edematous basal layer stained poorly, their nuclei having undergone varying degrees of pyknosis. The venous channels of the superficial decidua were engorged with blood, some thrombosed, and the stroma was heavily infiltrated with round cells and multiple small hemorrhages. The placental villi appeared normal in histologic section.

Comment

The endometrial reaction in pregnancy embraces a series of elaborate and continuing changes involving the glands, stroma, and blood vessels. Some of these alterations, such as the decidual stromal response and gestational glandular development, clearly reflect hormonal stimulation. Others, such as coagulation necrosis in the decidua basalis and attenuation of the decidua vera, probably result from local chemical and mechanical influences of the trophoblast and fetal sac, respectively. Separate evaluation of each of these three major forces acting on the uterine decidua is impossible in normal pregnancy, for all coexist in time and place. Ectopic pregnancy, on the other hand, creates an experiment of nature in which the purely hormonal effects on the endometrium can be cleanly differentiated from the locally invasive activity of the trophoblast and the pressure of the gestation sac. Hysterectomy specimens from patients with ectopic pregnancies of varying duration thus reveal the natural history of the hormone-stimulated gestational decidua unaffected by other factors.

In the present series of cases, ranging from the fifth week to full-term ectopic pregnancy, the thickness of the uterine decidua as measured in fixed section varied sixfold, from a minimum of 2.2 mm. to a maximum of 1.4 cm.; but this measurement could not be correlated with the stage of gestation, both the thickest and the thinnest membranes being observed in pregnancies of almost identical duration (Cases 2 and 5). Nor could any relation be established

between the thickness of the decidua and the viability or death of the trophoblast, although in 2 cases of death of the trophoblast (Cases 3 and 8) the decidua had sloughed away and the endometrium reverted to its nonpregnant condition. The significant changes in the decidua were limited to qualitative alterations in the endometrial components.

Pronounced stimulation of both epithelium and stroma was apparent in the endometrium of the earliest specimens, from the first 12 weeks. The glands showed excellent gestational development and secretory activity, and the stroma its full decidual response. In some cases the glandular elements predominated and only in the superficial part of the compacta was an extensive sheet of decidual stroma conspicuous; whereas in other cases of similarly early stage the relations appeared reversed, with decidual stroma occupying most of the field. Even in the earliest specimens partial exhaustion of glandular secretory function was apparent. By the twentieth week secretory exhaustion was nearly complete, most of the glands showed partial atrophy, and the bulk of the endometrium consisted of broad masses of transformed connective tissue. Sections of the uterus at later stages showed an even greater disparity between glands and stroma, the term specimen containing only a few slitlike structures, completely devoid of secretory activity. This dissociation of the stromal from the glandular reaction may indicate a qualitative or quantitative difference in the hormone requirement of the two types of tissue, or, more probably, an inherent inability of the differentiated endometrium to maintain its secretory activity for prolonged periods. It has also been suggested that the decidual cells undergo continuous replacement and perhaps augmentation during pregnancy, an advantage denied the exhausted secretory epithelium.

The integrity of the uterine decidual stroma and its delicate reticular framework is maintained to full term in ectopic pregnancy or until death of the conceptus occurs. Dissolution of the reticulum, increased leukocytic infiltration, and beginning autolysis and slough of the superficial decidua may be seen in 2 of the 4 cases (1 and 9) in the present series in which the fetus had died previously or the trophoblast was no longer viable. In the 2 other cases (3 and 8) of death of the trophoblast the uterine decidua had already been replaced by a cyclic, nonpregnant endometrium. Each of the 8 patients with histologically viable trophoblast also had an intact uterine decidua. Only in Case 12, at full term, were diffuse, early degenerative changes in the decidual cells apparent, together with interstitial hemorrhage and vascular thrombosis. The suggestion is inescapable that these decidual changes, hormonally determined, underlie the onset of labor in normal intrauterine pregnancy.

The superficial veins of the endometrium undergo striking dilatation at a very early stage of normal gestation, beginning with implantation of the trophoblast. As the placenta develops, these dilated venous channels become the basal and lateral sinuses and the intervillous space. This important adaptation, likewise conditioned by humoral influences, is activated independently of the trophoblast's location, as shown by the huge superficial vascular sinusoids in Case 4. In the present material, dilated and branching venous channels comprised a prominent feature of the decidua throughout pregnancy, but in the absence of a uterine implantation the pronounced vascular dilatation in the compacta failed to persist beyond the early stage.

Vaginal bleeding, it will be noted, occurred in macroscopic proportions in 10 of the 12 cases, despite the apparent viability of the trophoblast in 8 of the former group and the subsequent survival of the fetus to the third trimester of pregnancy in 3. The conceptus was dead, on the other hand, in both cases where no vaginal bleeding had been observed during pregnancy. These data

clearly refute the notion that vaginal bleeding in ectopic pregnancy signifies fetal death. We have commented previously on the physiologic nature of bleeding in early intrauterine pregnancy.[30] A similar mechanism, homologous to the vascular phenomena of menstruation, probably prevails in ectopic gestation and mediates the decidual bleeding usually associated with this condition.

Summary

The endometrial changes in ectopic pregnancy, from 4½ weeks to full term, have been recorded from the study of 12 uteri removed without prior curettage; and the integrity of the decidua has been correlated with the histologic appearance of the trophoblast. The decidua of ectopic gestation reflects the purely hormonal influence of pregnancy, dissociated from the chemical action of the trophoblast and the pressure effect of the fetal sac. Great variations were observed in the thickness of the decidua but without relation to the stage of pregnancy or to the viability of the trophoblast. In 2 of the 4 cases in which the trophoblast was dead, the decidua had already been replaced by cyclic, nongestational endometrium. Pronounced dilatation of the superficial veins of the compacta characterized the decidua of early pregnancy. By the twelfth week most of the gestational glands had undergone secretory exhaustion, the decidua consisting chiefly of a broad sheet of transformed stroma. The integrity of the decidual stroma was maintained until full term or until death of the trophoblast, when dissolution of the reticulum, increased leukocytic infiltration, interstitial hemorrhage, vascular thrombosis, autolysis, and slough occurred. It is suggested that these decidual changes may initiate labor in normal intrauterine pregnancy. Vaginal bleeding in ectopic pregnancy, which was noted in 10 of the 12 cases and does not necessarily signify death of the fetus or trophoblast, may be regarded as the counterpart of the physiologic bleeding of intrauterine pregnancy, both probably resulting from the same vascular phenomena that produce the bleeding of menstruation.

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ECTOPIC PREGNANCY CAUSED BY SCHISTOSOMA HAEMATOBIUM INFECTION OF THE FALLOPIAN TUBE

A Case Report

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THIS is the case of Mrs. S. A. R., who was a 35-year-old gravida v, para iii, with a history of amenorrhea for one month followed by moderate vaginal bleeding for 20 days before she was first seen. She was referred to Bagdad by her physician in Karbala (a city 250 miles from Bagdad) on the evening of March 14, 1955. There was a history of increasingly severe acute abdominal pain associated with syncope that began 4 days before admission and had been treated with antibiotics by her physician who felt she had pelvic inflammatory disease.

Her past history, except for malaria, was uneventful. There was no history of hematuria. She had used no contraceptives but had had no pregnancies for 3½ years.

On initial examination the patient was found to be acutely ill, pale, and in severe distress. Her temperature was 38° C., pulse 96 per minute, and blood pressure 130/80.

Examination of the abdomen showed marked rigidity and rebound tenderness, especially in the left hypogastric area where a vague but extremely tender mass was felt below the level of the pelvic brim. There was limitation of abdominal movement with respiration and shifting dullness was present.

On pelvic examination the vagina and cervix were found to be softened. The uterus was of normal size, anteflexed, but displaced to the right with limitation on rotation. To the left and posterior to the uterus was a vague, tender, soft mass, 13 cm. in diameter.

The patient was immediately hospitalized in one of the private hospitals in Bagdad with the presumptive diagnosis of ectopic gestation. There her blood was typed and cross-matched, she was given premedication with morphine and scopolamine. In the operating room under ether and oxygen anesthesia the abdomen was opened with a paramedian incision. A large amount of free blood with clots was found in the peritoneal cavity and a ruptured tubal pregnancy of the ampullary part of the left tube was seen. A left salpingectomy was performed. After cleaning the peritoneal cavity the peritoneal surface of the uterus, bladder, pouch of Douglas, broad ligaments, tubes, and ovaries were found to be studded by small whitish spots that measured between 1 and 5 mm. in diameter. Some were calcified, projecting above the level of the peritoneum and some were soft, resembling miliary tuberculosis. The right tube was thick, hard, and fibrosed, but the fimbriated end was open. There were no adhesions to the neighboring organs. The abdomen was closed in layers.

The removed tube was sent to Dr. Y. Akrawi, Ph.D., for pathologic examination.

With a clinical gross diagnosis of tuberculous peritonitis the patient was placed on streptohydrazid, 1 Gm. per day.

The microscopic pathological diagnosis reported a tubal pregnancy of the ampullary portion of the tube secondary to marked fibrosis caused by the ova of *Schistosoma haematobium* surrounding the tube. The tubal wall was markedly thickened. The urine examination showed no *Schistosoma haematobium* eggs.

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The patient was then started on an antimony preparation, Fuadin, which is specific for bilharziasis. She was discharged on March 27, 1955, in good condition with a recommendation to her physician that Fuadin be continued.

Fig. 1.

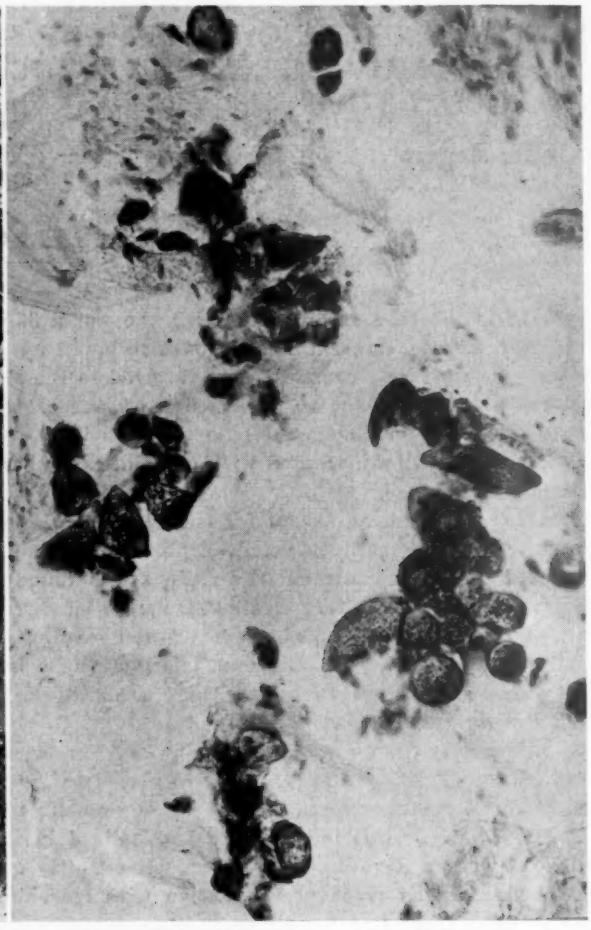

Fig. 2.

Fig. 1.—The affected tube with bilharzial ova shown by arrow. (Low power.)
Fig. 2.—The affected area with bilharzial ova. (High power.)

Comment

Schistosoma haematobium or urinary bilharziasis (related to Bilharz, 1852) is a disease caused by the presence of blood flukes, *Schistosoma haematobium,* in the vesical and pelvic venous plexus of man. The disease is usually accompanied by severe cystitis and hematuria. It is endemic in some parts of Southern Iraq.

It has a life cycle which is partially in man and partially in special kinds of snakes that live in fresh water.

The cycle is started by the embryonal eggs which are characterized by the presence of a spine and knob on the shell. The eggs, in the urine of infected man, may contaminate the water. They will hatch twice, forming the free-swimming ciliated larvae (miracidium) which will penetrate the snakes, *Bulinus planorbis,* in which it will pass through several generations in the host

tissues. A free living brevifurcate (short fork-tailed) cercaria will infect man through exposed skin in water, usually the feet, and then pass to the blood stream, developing into male and female worms or flukes. They usually are found in vesical and pelvic blood vessels, laying their eggs in the surrounding tissues.

The pathological changes are the reaction of the tissues to the presence of the eggs. In our case, where the eggs were layed in all the internal genitals, the reaction of those tissues to the presence of the eggs resulted in fibrosis and thickening. The Fallopian tubes were involved and were greatly thickened and narrow and partially obstructed, permitting the passage of the spermatozoa but not the bigger fertilized egg down to the uterine cavity; hence, the imprisoned fertilized egg implanted itself in the ampullary part of the tube causing the ectopic pregnancy.

Summary

The case is reported of a woman with secondary sterility of 3½ years' duration, who had *Schistosoma haematobium* infection of the internal genitals causing great thickening, fibrosis, and narrowing of the Fallopian tube. This resulted in a partial obstruction of the tube and ectopic pregnancy.

The patient did not give any history of hematuria or cystitis which is the most important symptom of the disease.

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PRIMARY OVARIAN PREGNANCY

Case Report

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OVARIAN pregnancy occurs statistically once in 25,000 pregnancies[1, 2, 3] and once in every 117 ectopic pregnancies.[1] The average age of women operated upon for ovarian pregnancy is 30 years and 75 per cent of such pregnancies are terminated in the first trimester.[1] That primary ovarian pregnancy is coming to be recognized more often is supported by many recent articles.[1, 4-7] As late as 1940, however, Novak[8] stated that there were only 50 authenticated cases reported, although Moulonguet,[9] in 1924, reported 77 cases. Strother-Stewart,[5] in 1953, reported there were at least 125 authenticated cases in the English literature. Apparently the acceptable incidence of this entity is less than 200 verified cases.

The criteria for true ovarian pregnancy were set forth first by Spiegelberg[10] in 1878. They are: (a) the tube must be normally intact and have no organic connection with the gestational sac, (b) the gestational sac definitely must occupy the normal anatomical position of the ovary, (c) the gestational sac must be connected with the uterus by the uteroovarian ligament, and (d) unquestionable ovarian tissue must be demonstrated in the walls of the sac.

Baden and Heins[1] noted confusion in the literature from the use of the diagnosis, "ovarian pregnancy." They suggested a more specific classification of "primary ovarian pregnancy," in which ovarian tissue forms an intact layer around the embryonic tissues, and "combined ovarian pregnancy," in which ovarian stroma forms a portion of the adjacent implantation tissue wall. The classification may be subdivided into: intrafollicular, in which the fertilized ovum is implanted and develops in the Graafian follicle, and extrafollicular, in which the ovum is implanted and develops in ovarian stroma.

This article presents a case of primary ovarian pregnancy, extrafollicular type, to be added to the growing list of authenticated cases.

Mrs. N. S. T., an 18-year-old white woman, para i, gravida iii, was first seen in the outpatient clinic on April 22, 1957, with the chief complaint of right lower quadrant pain.

Clinical History.—She had been delivered of a full-term normal infant on July 11, 1955. She had 2 early spontaneous abortions, each followed by curettage, in August and October, 1956.

Fig. 1.

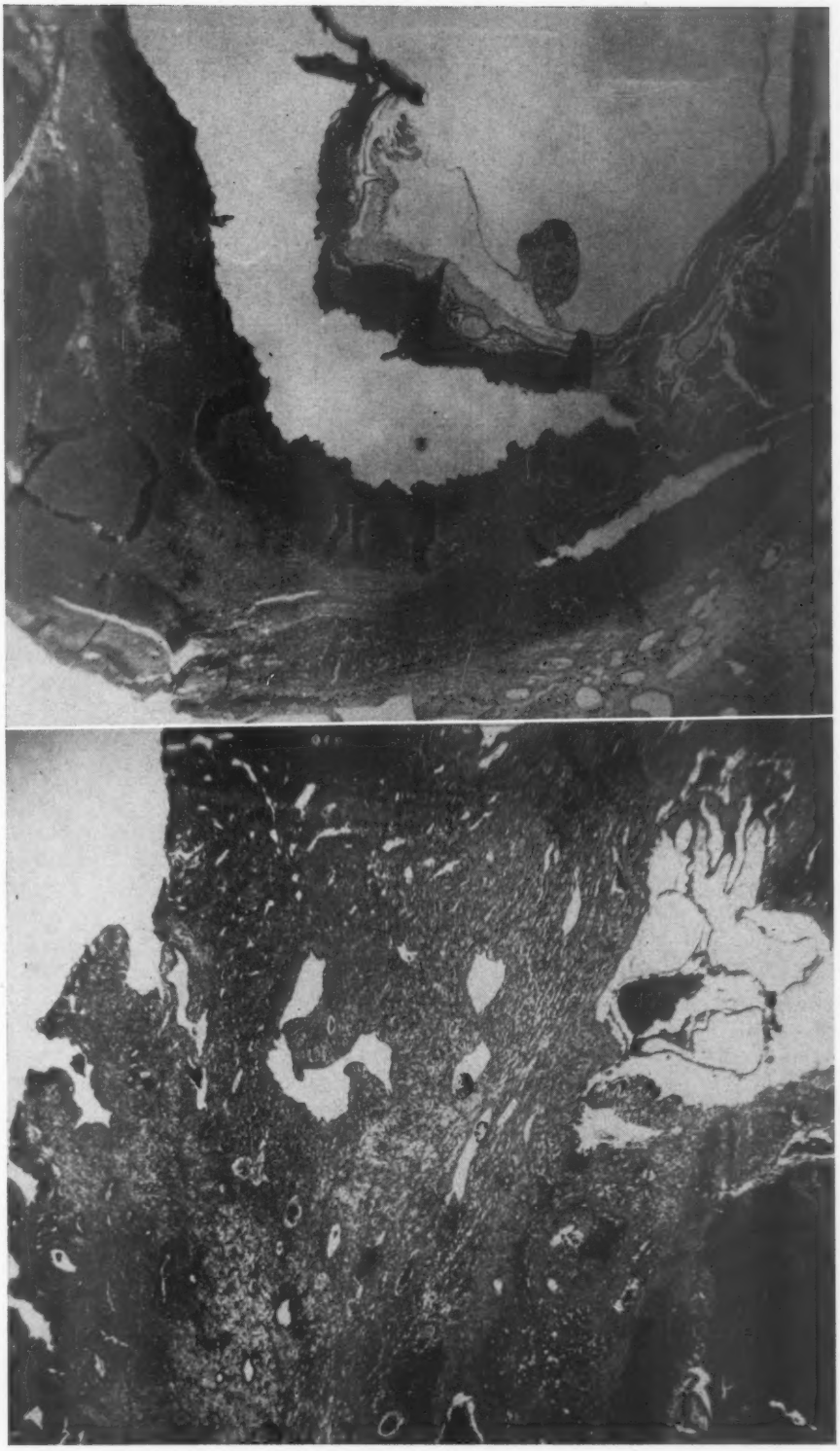

Fig. 2.

Fig. 1.—Ovary. Implantation within ovarian stroma. Amniotic sac and primitive embryo are present. (Hematoxylin and eosin. ×40.)

Fig. 2.—Ovarian tissue with decidual change and wall of implantation at margin. (×100.)

She gave a history of having had right lower quadrant pain during both of the last two gestations and a chronic low-grade pain in the right lower quadrant with acute exacerbations since October, 1956. The pain was aggravated by physical movement to the extent that she could not lift her infant without severe discomfort. Marked dyspareunia was present. There was no nausea, vomiting, dysuria, or change in bowel habits.

Menstrual bleeding lasted from one or 2 days to as long as 14 days with intermittent spotting and occurred at intervals of a few days to 3 weeks. Previously her periods had occurred at regular 28 to 30 day intervals. Her last menstrual period was on April 13, 1957, and was considered normal by the patient.

Physical examination revealed marked right lower quadrant tenderness upon motion of the cervix. An indefinite, exquisitely tender, cystic mass approximately 3 to 4 cm. in diameter was felt in the right adnexal region. The left ovary was also cystic but only slightly tender. A tentative diagnosis of right ovarian cyst or hydrosalpinx was made. The patient was sent home on analgesics with pelvic rest and advised to return for reevaluation in 2 weeks.

Two weeks later, on May 6, she reported persisting abdominal pain without change in character. Physical examination again disclosed the same cystic mass in the right adnexal area with marked pain on palpation. In view of the long history of menstrual irregularity and right lower quadrant pain out of proportion to pelvic findings, an exploratory laparotomy was indicated. The tentative differential diagnoses were twisted ovarian cyst, endometrioma, or hydrosalpinx.

Physical examination after hospitalization showed a thin young white woman who was apprehensive but in no apparent discomfort. She weighed 103 pounds and was 63 inches in height. Her blood pressure was 110/70. There were no outstanding physical findings other than those noted in the outpatient clinic. Laboratory reports showed the hemoglobin to be 12.3 Gm.; erythrocyte count 4.55 million; leukocyte count 8,300, with a normal differential. The Kahn test was negative and the urinalysis was within normal limits.

Findings at Laparotomy.—Operation was performed on May 10, 1957. There was no free blood in the peritoneal cavity. A normal-sized, freely movable uterus was noted. The left ovary was normal in size but contained a small cyst, from which approximately 6 c.c. of clear fluid was drained. The left tube was normal in size and free from any adhesions. The right ovary was normal in size but on the posterior lateral surface there was a hemorrhagic-appearing cyst measuring approximately 2 cm. by 2 cm. A slight amount of blood was noted on its surface. There were a few recently formed adhesions between the parametrial tissue and the ovary. The Fallopian tube was free of adhesions and was not congested. The fimbriated end appeared patent.

The hemorrhagic portion of the right ovary was excised, leaving an estimated 90 per cent of normal tissue. The free edges were approximated and sutured.

The patient had an uneventful postoperative course and was discharged from the hospital on the eighth postoperative day. She has been followed in the outpatient clinic with complete alleviation of all symptoms.

The specimen was sent to the laboratory with the clinical diagnosis of corpus hemorrhagicum.

Pathologic Description.—

Gross: The specimen consisted of an irregular cystic piece of ovarian tissue measuring 2.0 by 1.3 by 1.8 cm. The external surface was smooth and glistening, and had a dark, bluish-red discoloration. The cut surfaces showed a cyst with a thin fibrous wall, containing a dark-red, hemorrhagic-appearing material. Within the central area there was a small, clear, fluid-filled cystic space measuring 4 mm. in diameter.

Microscopic: The entire central portion of the specimen was composed of hemorrhagic decidual and placental tissue with chorionic villi, lined by a double layer of trophoblastic cells. The grossly described small cystic space was the amniotic sac. There

Fig. 3.

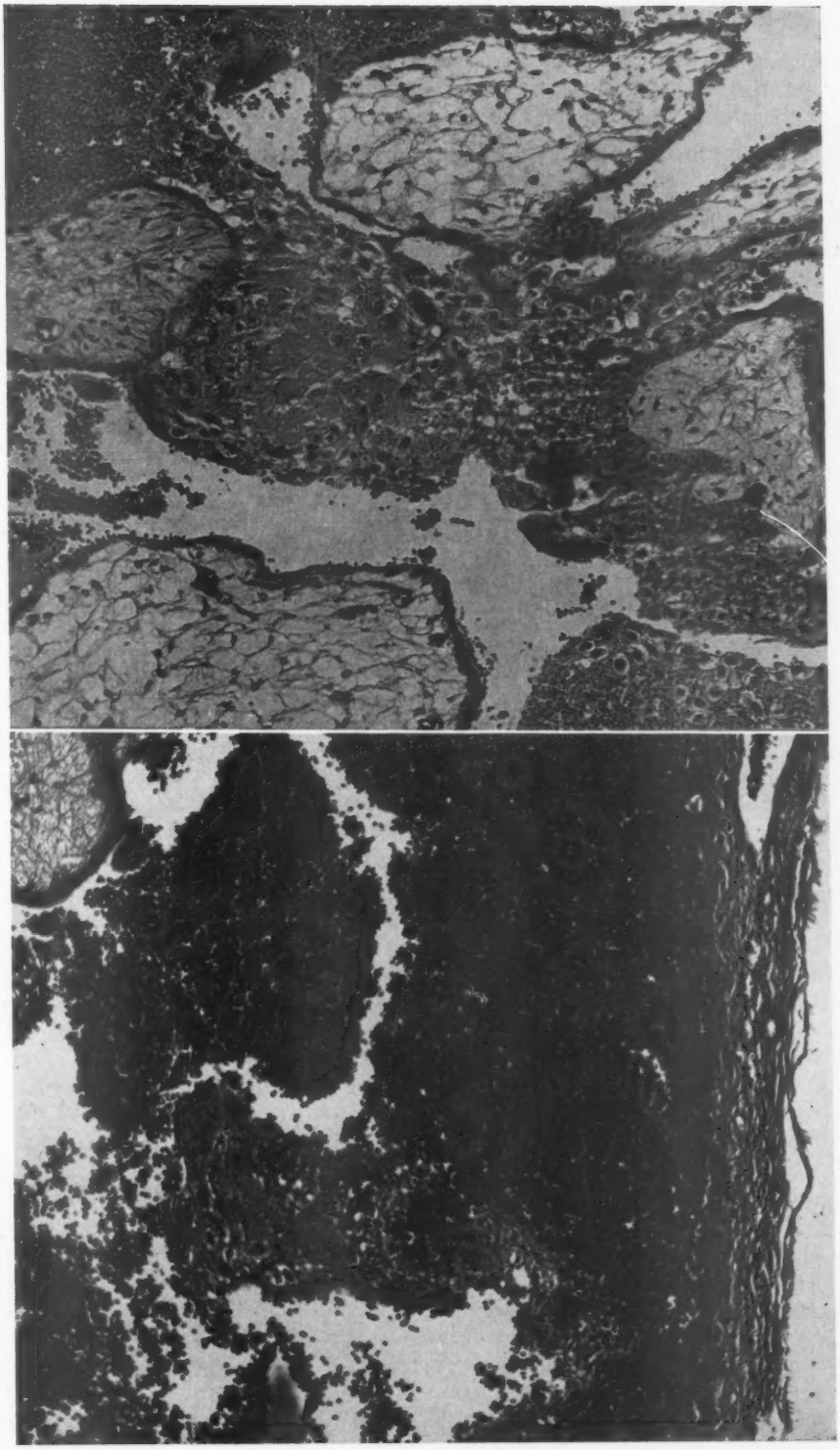

Fig. 4.

Fig. 3.—Chorionic villi, decidua, and recent hemorrhage within ovarian implantation. (×400.)

Fig. 4.—Outer wall of implantation tissue showing narrowest margin of intact ovarian stroma. (×400.)

was a narrow rim of ovarian tissue entirely surrounding the decidual and chorionic tissue. In one area of ovarian tissue there was an intact corpus luteum. The stroma adjacent to the implantation was infiltrated by moderate numbers of lymphocytes and an occasional histiocyte containing finely granular, yellow pigment.

Diagnosis.—Primary ovarian pregnancy, extrafollicular type, on the right.

Follow-up.—Clinical follow-up on this patient in January, 1958, disclosed an apparently normal pregnancy of 5 months' gestation. There was occasional vaginal bleeding with almost daily spotting during the first trimester which was under control at that time.

Summary

This report reviews the literature on primary ovarian pregnancy, briefly stressing the incidence, criteria, and classification. An additional authenticated case, meeting all the requirements of Spiegelberg, is presented.

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PRIMARY PERITONEAL PREGNANCY

Rationalization or Established Entity? Omental Transference as an Alternative Explanation

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AN ABDOMINAL pregnancy is designated primary or secondary according to the assumed site of primary nidation. The term "primary abdominal pregnancy," correctly used, embraces both primary ovarian[49] and peritoneal[50] pregnancies. Secondary abdominal pregnancy occurs when a fertilized ovum which has begun to develop elsewhere finally is reimplanted in the abdominal cavity. Although these are regarded as distinct pathologic entities, it may be impossible to differentiate between them in an advanced case. The clinical picture and treatment are essentially the same in all trimesters of pregnancy.

Abdominal pregnancy is not a rare condition. In 1876 Parry[41] collected 500 cases from the literature. By 1948, at least 578 cases of advanced extrauterine gestation had been reported.[20, 59] In Ware's[59] series of 249 cases collected from the literature from 1933 to 1946, the maternal mortality was about 15 per cent; of the 251 babies, 140 died in the abdomen and 50 within the first few days of life, giving a total fetal mortality of 75.6 per cent. Although the mortality figures have been reduced with the present treatment favoring early laparotomy, massive blood transfusion, antibiotics, and a healthy respect for placenta and sac adherent to abdominal viscera, this is still an extremely dangerous condition for mother and infant. From the foregoing, the importance of the subject is obvious and therefore it seems logical that we should strive to understand the pathogenesis of all postulated types of abdominal pregnancy.

Ovarian pregnancy is designated as primary or secondary according to whether or not the ovary is the site of primary nidation. Although advanced cases may present as abdominal pregnancies with the ovary involved in the placental site, it is obvious from anatomic consideration that these do not involve primary peritoneal nidation.

Secondary abdominal pregnancy most commonly follows tubal abortion or rupture. The essential feature in the pathogenesis of this entity is the maintenance of adequate nutrition for the growing fetus. This is most commonly achieved by rupture of the ovum with maintenance of the original placental site in the tube and escape of the attached embryo into the peritoneal cavity. Less frequently gradual extrusion of the ovum may occur. Here sufficient blood supply is retained from the original site of implantation until secondary placentation becomes established on an adjacent structure. Because of the precarious blood supply, the most common termination is death

of the ovum with resorption, mummification, or calcification, depending on the stage of gestation reached. If the pregnancy survives, extensive adhesions of the sac to the adjacent organs develop progressively, as do the vascular channels in association with the placenta. Thus, procrastination increases the formidability of the operative treatment required and, in the few cases where conservatism is justifiable, constant hospitalization of the patient is desirable. Intraligamentous pregnancy resulting from rupture of the tube or uterus is a special type of secondary abdominal pregnancy. It is more common than ovarian pregnancy and its pathogenesis is readily understood. It presents special features in that, as the gestation advances, the sac is related intimately with bladder and abdominal wall anteriorly, with sigmoid and rectum posteriorly, and with vagina and uterine body mesially.

Primary peritoneal pregnancy is one in which evidence of primary uterine, tubal, or ovarian nidation is absent and in which the site of implantation is related exclusively to the peritoneum. Consideration of the area of attachment involved in the implantation of a mature placenta, as well as its ability to migrate from its site of origin by proliferation in one area and atrophy in another, makes quite apparent the difficulty of determining the primary site of nidation in cases of advanced abdominal pregnancy, for even in cases of obvious secondary abdominal pregnancy, the site of implantation may be far from the pelvis.[13] Even the recent case of implantation of a 24 weeks' gestation on a leiomyofibroma reported by Kroupa and Bleicher[27] is suspect for this reason. A number of cases of advanced primary peritoneal pregnancy which reached term and even resulted in living infants have been reported.[3, 15, 54, 56]

Since many cases of ovarian and secondary abdominal pregnancy have resulted in live children, then if there is such an entity as primary peritoneal pregnancy, there seems to be no reason why some should not go to term. The assumption, however, that an abdominal pregnancy at term is of primary peritoneal origin, whether based on history, terminal site of placentation, or histologic study, appears to be scientifically unsound. Thus, the most rewarding field of research in this problem must necessarily be in the investigation of cases of early abdominal pregnancy. Within the abdominal cavity the only tissues available for implantation are the germinal epithelium of the ovary, the visceral and parietal peritoneum, and perhaps patches of ectopic endometrium.

In the past many authorities have denied the possibility of primary implantation in any tissue of non-Müllerian origin. Jarcho[24] quoted Robert Lawson Tait (1888), who first successfully operated for a tubal pregnancy, as stating, "that a fertilized ovum may drop into the cavity of the peritoneum and become developed there, is a contingency I cannot accept for a moment, for the powers of digestion of the peritoneum are so extraordinary that an ovum, even if fertilized, could have no chance of development." J. Bland Sutton[51] whose investigations of ectopic pregnancy in animals are well known, also denied the possibility of primary peritoneal pregnancy. According to these and other early investigators, all abdominal pregnancies other than ovarian were due to secondary implantation on the peritoneum following tubal abortion. As recently as 1947 Nicolson[38] invoked this theory to explain his case of "secondary abdominal pregnancy" although in many respects the case reported was similar to the acceptable case of primary peritoneal pregnancy reported by Myles.[36] Emil Novak[39] believed that such a mechanism is incredible, maintaining that the embryo could not retain its vitality long enough to become reimplanted on the peritoneum and would succumb the moment its separation from the tubal wall was complete. Others have expressed similar views.[5, 8, 12, 14, 30]

A critical review of the literature reveals that Galabin[16] in 1896 reported the first case of primary pertioneal pregnancy. This patient had a 10 weeks' ovum in the pouch of Douglas and died from hemorrhage after its removal. The site of implantation, uterus, tubes, and ovaries were carefully examined at autopsy and a committee of the London Obstetrical Society concluded that, while admitting the possibility of secondary implantation following early extrusion of the fertilized ovum, primary peritoneal pregnancy was the most probable diagnosis. Witthauer[61] in 1903 reported a case in which the tubes and ovaries appeared normal and the omentum showed chorionic villi and associated blood clot. Hirst and Knipe[21] in 1908 studied a patient in whom a 6-week-old ovum was found implanted on the posterior surface of the left broad ligament just above the left uterosacral ligament, with the uterus, tubes, and ovaries appearing normal. Elzey[12] described a case of about 10 weeks' developmental time in which implantation had occurred in the lesser peritoneal cavity. Apart from this very convincing case of his own, he also reviewed briefly the cases of Greene,[17] Nagel,[37] and Longley,[32] in which the implantation sites were the lumbar gutter, spleen, and retroperitoneal space, respectively. Jacques[22] reported a case in which by posterior colpotomy he delivered a 9 cm. fetus from a gestational sac on the posterior aspect of the bladder peritoneum 4 years following subtotal hysterectomy, bilateral salpingectomy, and right oophorectomy. Many other cases have been reported.[1, 4, 6, 9, 18, 19, 23, 26, 28, 29, 31, 34-36, 42-45, 47, 53, 58, 60] Studdiford's[50] case published in 1942, however, did more to strengthen the concept than any other. The site of implantation was the posterior aspect of the uterus in the region of the left cornu. Novak,[39] expressing some doubt in the first edition of his textbook, *Obstetric and Gynecologic Pathology,* stated in the third edition, "Until recently there has been much skepticism as to the possibility of the fertilized egg implanting itself on the pelvic peritoneum outside the genital canal, but the case reported in 1942 by Studdiford seems to establish the possibility beyond question." Eastman[11] likewise has given Studdiford's case full recognition. Studdiford's criteria for the diagnosis of primary peritoneal pregnancy are: "(1) that both tubes and ovaries are normal with no evidence of recent or remote injury, (2) the absence of any evidence of a uteroperitoneal fistula, and (3) the presence of a pregnancy related exclusively to the peritoneal surface and young enough to eliminate the possibility of secondary implantation following a primary nidation in the tube."

The following case which fulfills these criteria is reported.

A 28-year-old Negro woman, gravida i, para i, was seen in the emergency room of the Atlantic City Hospital at 6:30 P.M. on May 5, 1956. Her main complaint was of severe lower abdominal pain of 2 hours' duration. Her last normal menstrual period had been on March 1, 1956. Up to that time her periods had been normal, lasting 3 to 4 days and occurring regularly every 30 days. She had had no discharge or vaginal bleeding since her last menstrual period. She had been perfectly well until 2 weeks previously, when she began to have colicky lower abdominal pain, fairly well localized in the hypogastrium, but with associated right shoulder tip pain on the day of admission. About 2 hours prior to arrival at the hospital, the patient fainted in her bathroom at home and on regaining consciousness she had severe constant lower abdominal pain. She had no urinary symptoms, but had been rather constipated and had noted intermittent distention of the abdomen and weakness over the previous 2 weeks. Her past and family history was noncontributory. Her only pregnancy in 1951 resulted in the spontaneous delivery of a full-term normal child and the puerperium was uneventful.

Physical examination revealed an asthenic Negro woman with very pale mucosae. The temperature was 98° F. and the respiratory rate was 22 per minute with a pulse rate of 106 per minute. The abdomen was slightly distended with maximal tenderness, rebound and muscle guarding present over the lower abdomen. No abnormal masses were

found; no bowel sounds were present. The pulse was regular and of fair quality. The initial blood pressure was 80/30 mm. Hg. Systemic examination was essentially negative. Hematologic examination showed: hemoglobin 5.8 Gm. per cent; leukocyte count 16,750 per cubic millimeter with 80 per cent neutrophils, 19 per cent lymphocytes, and 1 per cent monocytes.

At 7:30 P.M. examination revealed a now tense, distended abdomen with generalized rebound tenderness. Pelvic examination disclosed marked bilateral tenderness on movement of the cervix. A fullness was noted in the posterior cul-de-sac, but no definite masses could be outlined. It was considered that neither culdocentesis nor colpotomy was indicated because there was obvious bleeding into the abdomen and immediate laparotomy was required.

The abdomen was opened through a median subumbilical incision, and was found to contain about 2,000 c.c. of blood. A mass was palpated in the region of the interstitial portion of the right tube. A clamp was applied across the right infundibulopelvic and right ovarian ligaments. The bleeding continued, however, from an area on the posterior surface of the uterus about 2 cm. below and medial to the insertion of the right tube. A small clotlike structure about 2 cm. in diameter found attached to this area was carefully removed by finger dissection, leaving a bleeding roughened bed. A small area covered with similar tissue was removed from the adjacent sigmoid mesentery. Right salpingo-oophorectomy was performed. The mass which had been palpated in the region of the interstitial portion of the right tube proved to be a large, loosely attached, and rather firm clot. The bleeding from the eroded area on the posterior surface of the uterus was controlled with some difficulty. No sac or embryo was recovered; this was either left free in the abdomen or evacuated unnoticed with the clotted blood. The patient's condition improved and after the uterus and left tube and ovary were found to be normal, the abdomen was closed in the usual manner.

On the first postoperative day, the abdomen was only slightly distended and some bowel sounds were present. Laboratory examination showed the hematocrit to be 32 per cent and the leukocyte count 11,200 per cubic millimeter.

Thereafter, the patient made an uneventful recovery. She was discharged well on the sixth postoperative day with a hematocrit of 38 per cent.

Pathologic Examination.—The resected tube and ovary were grossly normal.

A. Sections of Fallopian tube showed marked thickening of the endosalpingeal villi. These were heavily infiltrated with chronic inflammatory cells. The muscular portions of the wall were fibrotic, edematous, congested, and showed round-cell infiltration. No evidence of early placentation was present.

B. Sections of the ovary showed a true active corpus luteum. No evidence of ovarian gestation was found.

C. Sections from the hemorrhagic membranous-tissue mass taken from the posterior wall of the uterus represented without doubt gestational elements, namely, young chorionic villi and trophoblast.

D. A section corresponded to mesentery and showed typical fatty tissue with areas of hemorrhage and a single endometrial gland.

Thus in this case the pregnancy was related exclusively to the peritoneal surface. The ovaries and tubes appeared grossly normal with a corpus luteum present in the right ovary. No uteroperitoneal fistulas were found. Microscopic sections of the right tube showed some congestion, fibrosis, edema, and round-cell infiltration. The fimbriated end of the right tube appeared normal, so no sections were taken of this region. In retrospect it appears that in such a case as this it would be advisable to examine microscopically serial sections of all tubal tissue removed, whether normal in appearance or not.

It is concluded that this case satisfies the accepted criteria for early primary peritoneal pregnancy. The presence of pelvic endometriosis at the same time raises the possibility of primary implantation of the blastocyst in a patch of endometrium on the posterior surface of the uterus.

Comment

The study of this and one other case[7] led to the consideration of the following factors in an attempt to elucidate the pathogenesis of "primary peritoneal pregnancy."

1. The "Postmature" Ovum.—An ovum is not considered mature for fertilization until the second polar body has been extruded, which probably occurs most commonly in the lateral portion of the tube. It is possible that intratubal fertilization with reflux of the hours-old ovum may result in primary ovarian or peritoneal pregnancy. It seems more likely, however, that in these cases the ovum matures early and becomes fertilized within the abdominal cavity, thereafter failing to achieve entry through the tubal ostium. Thus, it appears that while the shedding of a "postmature" ovum by the ovary is probably rare, it may be an important factor in the pathogenesis of primary peritoneal or ovarian pregnancy.

2. Pelvic Endometriosis.—From the observations of Rock and Hertig[46] on fertilized ova in culture media it is reasonable to suppose that segmentation proceeds likewise in the peritoneal cavity, the ovum reaching the morula (eight-cell stage) within 48 hours and the blastocyst stage on the sixth day. The trophoblastic processes about this time begin their invasion of the maternal tissues to supply nutriment for the developing ovum. In normal intrauterine nidation the conversion of endometrium into decidua begins several days after implantation. Thus, a new source of nutrition is available when the endogenous food supply is exhausted. In this phase, the trophoblastic villi erode the maternal tissues, making the protein, fat, and carbohydrate stores of the decidual cells available to the developing ovum. Progressive destruction of the maternal tissues results in the formation of more and more intervillous spaces. Toward the end of the third week, hemochorial placentation is established and nutrition of the embryo is dependent upon the maternal blood circulating in the choriodecidual space. In extrauterine gestation, where decidua even if present is generally inadequate, the trophoblast invades the deeper tissues in search of nourishment. Thus, it may invade the muscular wall of the tube, the ovarian stroma, or the subperitoneal connective tissues according to the site of implantation. These tissues are, of course, unsuitable for implantation, for they lack capillary sinuses such as are found in the uterine wall and the trophoblastic processes soon erode arterioles where the blood pressure is relatively high. The subsequent hemorrhage will usually separate the ovum from its bed and it seems unlikely that many will survive this catastrophe.

Survival would be more likely where implantation has occurred on a patch of ectopic endometrium, for here would be available a decidual food store to tide the early ovum over the first 2 to 3 weeks of life, and allow the gradual establishment of hemochorial placentation. The first 20 days of life is probably the most critical period for the ectopically implanted ovum. The frequent occurrence of endometrial tissue in the ovary may well explain why, as compared with tubal pregnancy, a relatively large proportion of ovarian pregnancies go to term. Decidual reaction in islands of endometriosis has been described by Velasco[57] and indeed, according to Ober and associates,[40] the presence of ectopic decidua is not uncommon even in the absence of pregnancy. Several authors[2, 8, 10, 24, 52] have commented upon the association of endometriosis with extrauterine gestation and Vara[55] has described a case of primary peritoneal pregnancy in a focus of endometriosis. According to Elzey,[12] when investigated in abdominal pregnancy, decidua-like tissue is invariably present in the vicinity of the placenta. Thus it appears that, in secondary abdominal pregnancy, either endometrium is available for decidua

formation or other adjacent tissue derived from subcelomic mesenchyme is converted into decidua. If primary peritoneal pregnancy does occur, the ovum is more likely to survive where good decidua is available, for early nutrition is an urgent problem. Although it seems likely that a better quality of decidua will arise more quickly in ectopic endometrium, the ovum may survive by taking advantage of decidual change in the subperitoneal stromal cells.

3. Experimental Evidence.—Little experimental evidence could be found in support of the concept of primary peritoneal pregnancy. Although the secondary variety has been frequently reported in rabbits and dogs, primary peritoneal nidation has not apparently been observed. Sittner[48] transplanted two 8 day rabbit ova from intrauterine to intra-abdominal sites. Autopsy later showed that the ova had not only survived transplantation but had continued to develop as they would have in utero. This experiment tends to support the "modern" view that nidation of the ovum may occur in any tissue irrespective of its embryonic derivation. As pointed out by Baldwin,[4] however, surgical grafting is not quite the same as spontaneous implantation. Furthermore, it may be fairly argued that an 8 day rabbit ovum may be more capable of survival than a human ovum under the same circumstances.

4. Clinical Evidence.—Clinical evidence for the concept of primary peritoneal nidation has taken three main forms:

A. Discreditation of the old tubal abortion theory, which held that the postabortal ovum lying free within the peritoneal cavity, and perhaps floating in blood, could retain enough vitality to be reimplanted. It certainly seems unlikely that an ovum which has reached the hemochorial stage could survive while re-establishment of its nutritional channels is being carried out. In support of this view is the fact that no case of secondary abdominal pregnancy has ever been reported as a result of failure to recover an embryo from the abdomen at laparotomy for a ruptured tubal pregnancy.

B. Consideration of the ability of the growing placenta to invade visceral and parietal peritoneum as seen in advanced cases of abdominal pregnancy. Since the mechanism of implantation of the trophoblast is the same regardless of site, it has been argued that this is evidence for the ability of the ovum to become implanted primarily on the peritoneum. The validity of this argument may be challenged on the ground that it may be essential for chorionic villi to have acquired a certain maturity before they can effect adequate implantation on non-Müllerian tissues. Furthermore, whereas the mature placenta has ample time to settle and establish nutrition, rapid implantation is a vital necessity for the early ovum and it may well be incapable of this on barren peritoneum.

C. Presentation of sufficient cases meeting the accepted criteria to elevate the status of this hypothesis to what most authors consider an established entity. The necessity for criteria was first recognized by Hirst and Knipe[21] in 1908 and they suggested that in any true case the peritoneum would be the reflexa of the ovum. (Their case is the only one in the literature which apparently meets this criterion.) Jacquin[23] in 1922, Best[6] in 1931, and Studdiford[50] in 1942 reviewed the criteria and those of the latter have now become almost universally accepted.

Studdiford's criteria are difficult to meet and certainly have gone a long way in excluding doubtful cases, but more critical evaluation yet would be required to establish the concept beyond doubt. Thus, although both tubes and ovaries may appear normal and without evidence of recent or remote

injury, important defects may be missed. Serial sections of both tubes and ovaries with careful microscopic examination would be required before abnormalities could be excluded. Thus, in the case reported here, the tube showed edematous changes and round-cell infiltration, although to the naked eye the tube appeared normal. Some may argue that rupture of the tube had taken place at this site at an earlier stage, and although this seems unlikely the possibility cannot be denied. So far as can be ascertained from the literature on the subject a complete microscopic examination of both adnexa has never been undertaken in any reported case. Careful autopsy examination of a case, such as that reported by Galabin,[16] with microscopic sections of the pregnancy site, ovum, uterus, tubes, and ovaries would, of course, probably give the final answer to this problem. It is possible that a case of peritoneal pregnancy will be found in which, because of other lesions, total hysterectomy and bilateral salpingo-oophorectomy will be performed. Until then, there will be a possibility of error in the assessment of the internal genitals, dependent upon the eyesight, experience, and integrity of the individual author.

Furthermore, there may be no obvious uteroperitoneal fistula and yet the ovum could have escaped from the uterine cavity or tube via a fistulous tract no longer visible. Here even serial microscopic sections may fail to reveal the aperture.

Finally, Studdiford[50] pointed out that the pregnancy should be related exclusively to the peritoneal surface and yet be young enough to eliminate the possibility of secondary implantation following a primary nidation in the tube. This criterion is frequently ignored by authors claiming primary peritoneal pregnancies, although, as pointed out previously, real evidence of the entity is most likely to be found in early cases. Yet other authors have introduced an untenable criterion which assumes that the possibility of primary nidation is directly proportional to the distance of the placental site from the genital tract and have reported cases on this basis.

The rapidly increasing number of case reports on primary peritoneal pregnancy has added fuel to the fire of this concept. After a critical review of the literature, however, it becomes amply clear that most of the flame comes from the quantity rather than from the quality of the logs. A great many of the cases reported are based on very flimsy evidence. Furthermore, no case could be found which proved the concept beyond doubt. As long as there is doubt, then there is room for further speculation. It is interesting to note that, of the many popular American and British textbooks consulted, only Lull and Kimbrough[33] suggested that primary nidation in the peritoneal cavity was still in doubt. In accordance with the natural desire to be regarded as something other than an intellectual vandal, it is incumbent upon any author challenging an accepted concept to suggest an acceptable alternative.

5. The Possible Importance of an Omental Transference Mechanism.—Tubal pregnancy is common, occurring once for each 53 births in Jackson Memorial Hospital, Miami, during the period July 1, 1955, to July 1, 1957. It is generally recognized that tubal abortion is the commonest termination, especially when the primary site of nidation of the ovum is in the ampullary portion of the tube. Furthermore, the clinical picture in tubal abortion is much more variable than that seen in tubal rupture, and, in fact, the pains experienced as the ovum is extruded gradually from the tube may be spaced widely apart and the patient suffers little discomfort. Even on direct questioning, patients who have definite secondary abdominal pregnancy frequently admit of no symptoms suggestive of tubal abortion. Thus, tubal abortion may occur with minimal symptoms, particularly if a tubal ampullary pregnancy is extruded gradually.

At laparotomy for ectopic pregnancy, it is common to see the omentum wrapped around the bleeding fimbriated end of a tube from which an aborting ovum is being expelled. Provided that the process of extrusion is gradual, does it not then seem likely that the ovum while yet receiving nutrition from its tubal attachment may be secondarily implanted on the omentum? The ovum may then lose its attachment to the tube and be carried off by the omentum, there to remain as an omental pregnancy. "Primary" omental implantations have been reported by several authors[31, 42, 61] and it is interesting to note that, in 3 of the 4 cases of rupture of a cesarean scar reported by King,[25] the ovum had become implanted upon the omentum filling the uterine defect.

After secondary omental implantation is established, the ovum may be transferred gradually to any part of the abdominal cavity either completely or in part. Complete transference may occur in which case the pregnancy in this tertiary site of implantation may present a convincing picture of primary peritoneal nidation in any part of the upper or lower abdomen. This mechanism could even explain Elzey's[12] case, which is one of the most convincing in the literature. In this patient, it is possible that the fertilized ovum became implanted primarily in the ampullary portion of the tube and was gradually extruded to be implanted secondarily on the omentum. Transference to the transverse mesocolon would then be readily understandable, the final step being the erosive action of the chorionic villi through the mesocolon, so that further development took place within the lesser peritoneal sac.

On application of this theory of omental transference of the ovum to other well-documented cases, it seems likely that many, if not all, could be explained on the basis of this mechanism. Furthermore, it explains more satisfactorily than migration of the placenta why the placental site is frequently far removed from the genital tract in cases of abdominal pregnancy.

Summary

1. The types of abdominal pregnancy are defined as:

a. Primary: (1) ovarian, (2) peritoneal.

b. Secondary, occurring subsequent to primary tubal or intrauterine pregnancy and including intraligamentous and secondary ovarian pregnancies.

2. The importance of abdominal pregnancy in regard to maternal and fetal mortality is emphasized; it is felt that we should strive for a better understanding of the pathogenesis in all varieties of extrauterine gestation.

3. The importance of early cases in the study of the pathogenesis of primary peritoneal pregnancy is explained.

4. A critical review of the literature on primary peritoneal pregnancy with accepted views on its present status is given. Studdiford's criteria are enumerated.

5. A case is reported which apparently fulfills these criteria.

6. The possible part played by the "postmature ovum" and pelvic endometriosis in the pathogenesis of primary peritoneal pregnancy is discussed. Experimental evidence for the concept is lacking. Clinical evidence is only as strong as the cases reported and many of these are far from convincing.

7. The adequacy of the present criteria for diagnosis is questioned and the difficulty in proving the concept beyond doubt is inferred.

8. An alternative theory of "omental transference" is suggested which may explain many, if not all, of the well-documented cases of "primary peritoneal pregnancy" reported to date.

9. It is concluded that although primary peritoneal pregnancy may occur, it is certainly not an established entity and many, if not all, of the cases reported to date may be secondary abdominal pregnancies.

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UNILATERAL TUBAL TWIN PREGNANCY

Report of a Case Possibly Involving Dizygotic Twins

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UNILATERAL tubal twin pregnancy is rare. Only 81 well-authenticated cases had been reported up to Dec. 31, 1957, including one of the interstitial variety.[1] The following additional case is reported.

Mrs. A. M., a 40-year-old Negro gravida viii, para vii, was seen in the emergency room of Jackson Memorial Hospital on Dec. 30, 1957, with the chief complaint of lower abdominal pain of 16 hours' duration. She stated that her last normal menstrual period had been in mid-September, 1957. In October and November the menses lasted only 2 days instead of the usual 7 days. During December the patient had experienced only intermittent vaginal spotting for 2 weeks prior to coming to the hospital. During these 2 weeks she had also noted mild intermittent crampy lower abdominal pains. On the night prior to admission, the pain suddenly became more severe and constant and some urgency and frequency were present. At one time she almost fainted in the bathroom.

The only pertinent past history was an episode of acute pelvic inflammatory disease treated by her physician with "shots" 15 years previously.

Examination in the emergency room showed a somewhat obese Negro woman in mild distress. Her blood pressure was 120/80, pulse rate 80 per minute, and temperature 98.6° F. Palpation of the abdomen revealed diffuse lower abdominal tenderness somewhat more marked on the left. Peristalsis was normal. No masses were noted. On pelvic examination the vagina contained some dark blood which seemed to be oozing from the cervical os. The cervix was soft with a small erosion and pain was felt on manipulation. The uterus appeared to be of normal size. No adnexal masses could be outlined because of tenderness. Culdocentesis was performed and 10 c.c. of nonclotting blood obtained. With this confirmation of the clinical impression of ectopic pregnancy, the patient was scheduled for laparotomy. One thousand cubic centimeters of blood was given immediately to correct the existing anemia.

At operation there was about 250 c.c. of unclotted blood in the peritoneal cavity. A ruptured ectopic pregnancy was present in the mid-portion of the left tube. A left salpingo-oophorectomy and appendectomy were carried out. The patient's vital signs were normal at all times. The postoperative recovery was uneventful.

The material received in the pathology laboratory consisted of a tube and ovary weighing 45 grams. The ovary measured 3.5 by 3 by 3 cm. and on transverse sectioning there were 2 corpora lutea measuring 1.6 cm. and 1.4 cm. in diameter, respectively. The tube measured 6 cm. in length and in its mid-portion the maximum diameter was 3.5 cm. About 2 cm. from the distal end there was a 1 by 2 cm. opening with clotted blood and placental tissue present. In the center of the clotted blood there was a cystic space measuring 2 cm. in diameter in which there were 2 embryos, each measuring 0.5 cm. in length. Microscopic sections confirmed the above data.

Final diagnosis: Left Fallopian tube: ruptured ectopic pregnancy (twin embryos, gestation approximately 6 weeks). Ovary: corpora lutea of pregnancy.

Comment

The first case of unilateral tubal twin pregnancy was reported by de Ott[4] in 1891. Since then at least 81 well-authenticated cases have been reported and the literature on the subject reviewed by several authors.[1, 6, 10, 13, 18] Trolle[17] estimated that about 100 cases had been described up to 1948 but gave no details in support of his contention. At least 2 cases have been reported in which a unilateral tubal twin pregnancy was combined with a simultaneous contralateral gestation.[2, 11] Unilateral triplet tubal pregnancy has been reported three times.[5, 9, 12] Included in this category also should be Vine's[19] case which was apparently a triplet tubal pregnancy in which the placenta retained its attachment to the fimbriated end of an otherwise normal right tube following rupture of the ovum. A case of quintuplet tubal pregnancy was reported by Treub[16] in 1910.

Bilateral simultaneous ectopic pregnancy is rare, only 140 cases being found acceptable from the literature by Stewart[15] in 1950. According to other authors[3, 14] only 96 cases of concurrent bilateral tubal pregnancy have been reported to date, and it is generally agreed that this represents the rarest type of double-ovum twin pregnancy. Apparently monozygotic twins occur more commonly in tubal than in uterine pregnancy. Arey[1] has suggested that in view of implantation difficulties the rate of growth of the ovum is so retarded that two embryonic areas develop instead of one. It has generally been accepted that all the cases of unilateral twin tubal pregnancy have been monozygotic and only 2 cases[8, 17] involving dizygotic twins have been described. The main basis for postulating dizygotic origin in these cases was the apparent age difference of the embryos but, of course, superfetation has never been proved in human beings and the differential growth rate may have been influenced by other factors. In our own case section of the adjacent ovary showed two distinct corpora lutea; both embryos were of the same size and development but this does not exclude the possibility that the present case was one of dizygotic twin tubal pregnancy. As a general rule the diagnosis of unilateral twin tubal pregnancy cannot be made preoperatively. The presence of an adnexal mass of size disproportionate to the duration of amenorrhea, in a patient with a strong family history of multiple births, may suggest the possibility. Almost invariably, however, the diagnosis is made at operation, and of course the management is identical with that for single tubal pregnancy. Comparison of reported cases of unilateral tubal twin pregnancy with several series of single tubal pregnancies shows no significant difference in maternal prognosis when corrected for the era of occurrence.

Summary

Up to Dec. 31, 1957, only 81 well-authenticated cases of unilateral tubal twin pregnancy had been reported. A further case is reported in which the adjacent ovary contained two distinct corpora lutea, suggesting the possibility of a tubal dizygotic twin pregnancy.

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COMBINED TUBAL AND INTRAUTERINE PREGNANCY

A Case Report

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SIMULTANEOUS intra- and extrauterine pregnancies, otherwise known as heterotopic or combined pregnancies, have long attracted the attention of the medical profession. Novak[1] reviewed the 276 cases in the literature in 1926. Gemmell and Murray,[2] however, in 1933, accepted only 217 of these as being true simultaneous intra- and extrauterine pregnancies. In 1952, Zarou and Sy[3] brought the total up to 415 with their review and reported cases. Viviano[4] (1954) cited a total of 437 cases. Subsequent reviews and additions by Vasicka and Grable[5] (1956) bring the total to 435.

DeVoe and Pratt[6] estimated that simultaneous intra- and extrauterine pregnancies occur in 0.8 per cent of all ectopic pregnancies, and the latter occur in 0.37 per cent of all pregnancies. This, according to them, would mean an incidence of 0.003 per cent, or 105 cases out of 3.5 million pregnancies. Faxon[7] estimated that 10 per cent of all such cases result from intrauterine pregnancies superimposed upon already present ectopic pregnancies.

Simultaneous intra- and extrauterine pregnancies occur most frequently in older multiparas. In a study of 170 cases, Lawrence and Elsemore[8] reported that 67.8 per cent of the patients were 26 years old or older, and in DeVoe's series 70 per cent were multiparas (15 per cent primigravidas and 16 per cent unknown).

The mortality rate is rather high. Muller[9] cited a mortality rate of 61 per cent of the intrauterine fetuses and a maternal mortality of 21 per cent, in a study of 202 cases. Novak[1] listed only 9 of the 276 cases as resulting in extrauterine infants. Similarly, of the 22 cases reported by Zarou and Sy,[3] only 2 were known to result in survival of both infants.

On April 19, 1957, a 32-year-old white woman was admitted to the Two Rivers Municipal Hospital with the complaint of severe pain in the lower abdominal region which first occurred at noon on the day of admission. The last monthly period had been on Feb. 8, 1957, and since then there had been no bleeding.

A week before, examination had shown the patient to be about 2 months pregnant. Previously she had had 3 children, their ages ranging from 14 years to 8½ months.

Physical examination disclosed an acutely ill, pale woman with abdominal pain and marked tenderness in both lower abdominal quadrants. The pulse rate was 94, but regular.

The temperature was 99.6° F. and the blood pressure was 90/50. The lungs were clear and resonant. Pelvic examination demonstrated an acutely tender cervix, and a mass in the left adnexal region.

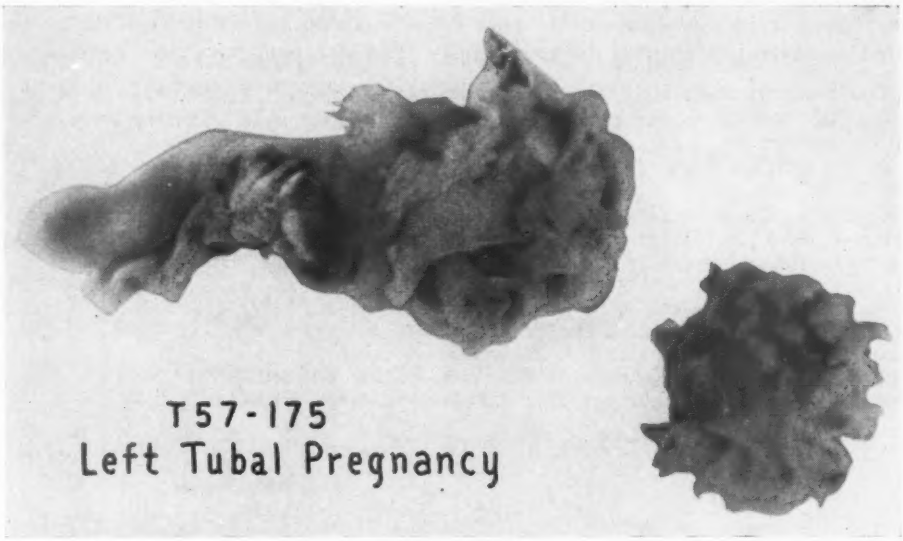

Fig. 1.

Fig. 2.

A diagnosis of a ruptured left tubal pregnancy was made. At operation the left tube was found to be ruptured (Fig. 1) and there was about 2,500 c.c. of blood in the peritoneal cavity. The uterus was enlarged to twice normal size. The right tube was normal. A left

salpingectomy was performed. Postoperatively, the condition was satisfactory. The pathology report was ruptured tubal ectopic pregnancy. On April 22, 1957, 48 hours after the operation, the patient started bleeding profusely and passed large clots. A curettage was performed. At the time of curettage the vagina was found to be full of clots and placental tissue. The cervix was dilated. A small fetus was removed (Fig. 2). The uterus was curetted and then packed with iodoform gauze. The postoperative course was uneventful.

The preoperative diagnosis of simultaneous intra- and extrauterine pregnancies is rarely made. In only about 4 to 10 per cent of the cases is it made correctly.

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ABDOMINAL PREGNANCY FOLLOWED BY ELIMINATION OF THE PLACENTA THROUGH THE BLADDER

Case Report

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THE following case is thought to illustrate several unusual complications of abdominal pregnancy.

A 36-year-old gravida vi, para v (No. 89527), whose last menstrual period was on Dec. 24, 1954, was admitted to Hahnemann Hospital Obstetrical Service after 35 weeks of amenorrhea, complaining of nausea, vomiting, severe abdominal pain, and obstipation of 7 days' duration, and leg cramps for 48 hours.

The patient had had an appendectomy at age 33. After 3½ months' amenorrhea she had been admitted to an out-of-state hospital because of severe right lower quadrant abdominal pain and pain in the right shoulder, and an ectopic pregnancy was considered. The pain, however, subsided, and she was discharged after 9 days.

On admission to Hahnemann Hospital, the patient was found to be hypotensive, pyretic, anuric, and in an advanced state of dehydration. The abdomen was distended, tympanitic, and diffusely tender. Auscultation failed to reveal evidence of peristalsis. A fetus of fair size could be palpated in a transverse lie. Fetal movements were distinct and the fetal heart rate was regular at 150 per minute.

A few cubic centimeters of almost black urine were obtained by catheterization of the bladder.

Vaginal examination disclosed the cervix to be hypertrophied and extremely soft. The external os and canal admitted a finger; the internal os was patulous. No membranes or fetal parts were palpated. The uterine body was difficult to outline but was felt to lie to the right of the midline and to be the size of a 12 to 14 weeks' gestation.

The provisional diagnosis was (1) secondary abdominal pregnancy at 35 weeks' gestation, living baby; (2) bowel obstruction, probably high ileal or low jejunal, secondary to the abdominal pregnancy or the old appendectomy; (3) lower nephron nephrosis; (4) marked dehydration, electrolyte and protein imbalance.

The flat plate of the abdomen was thought to show an intrauterine pregnancy, transverse lie, placenta located on the left uterine wall, and small bowel obstruction.

The patient improved rapidly under conservative therapy and 5 days after admission was operated upon.

When the abdomen had been opened, loops of distended small intestine were encountered. The intestine was in good condition, however. The easily recognizable amniotic sac was opened and a living, 4 pound, 8 ounce male child in good condition was delivered. The baby is still living, and to date no congenital abnormalities have been demonstrated. The umbilical cord was doubly ligated with cord tape close to the placenta.

The placenta, which was huge, was attached to the mesentery of the small and large intestines over a large area above, and below to the pelvic organs. No attempt was made to investigate its attachments in the pelvis or to ascertain the status of the pelvic organs. Several loops of small intestine were firmly adherent to the placenta deep in the abdominal cavity. No attempt was made to loosen these loops even though it was realized that they were partially obstructed. There was absolutely no blood loss.

The patient did well in the immediate postoperative period. However, attempts at oral feeding resulted in nausea, vomiting, abdominal distention, and pain.

Therefore, 10 days following the original abdominal section, the patient was reoperated upon because of failure to improve clinically under conservative therapy, and x-ray evidence suspicious of a closed-loop obstruction.

At operation, the small intestine was markedly distended and pale. There was no evidence of loss of its basic blood supply. The intestinal obstruction was the result of two segments of ileum, one 3 cm. and the other 8 cm. in length, being incorporated in the placenta where the placenta's lower pole was attached to structures in the pelvis. The intestine, although markedly narrowed, was intact, viable, and permitted the passage of gas through its narrowed lumen when separated by blunt and sharp dissection from its placental attachment. The separation of the obstructed intestine resulted in a loss of approximately 400 c.c. of blood. Further blood loss was controlled by placing a large pack against the lower portion of the placenta. No attempt was made to explore the abdomen or pelvis. The condition of the placenta was truly amazing. It was an unusually viable organ. Huge vessels on the fetal surface revealed little or no evidence of thrombosis.

The patient's course during the following 3 weeks was stormy. The abdominal distention persisted. Periodic bouts of abdominal pain recurred, associated with nausea and inability to retain liquids when the Wangensteen suction was disconnected. The patient finally recovered and was discharged 44 days following admission. On discharge, there was a minimal amount of drainage from a sinus at the site of the previously placed hemostatic pack.

Follow-Up.—When seen 2 months later, the patient had not regained her prepregnancy weight. She had no appetite and complained of periodic abdominal pain in the region of the still draining abdominal sinus. During these attacks of pain, the abdominal sinus would discharge "tissue resembling afterbirth." On two occasions she passed similar tissue in the urine.

With the exception of a draining sinus, the only positive abdominopelvic finding was an indefinite, soft, nontender mass just to the left of the midline, above Poupart's ligament.

The mass measured approximately 6 to 8 cm. in diameter and was considered to be the residual placenta.

A complete gastrointestinal x-ray series including opaque enema was negative.

An intravenous urogram showed normal kidneys and ureters and evidence suggesting an abdominovesical fistula, which suspicion was verified by cystograms and cystoscopy.

The patient was discharged from the hospital after 10 days, still periodically expelling placental tissue from the abdominal sinus and bladder.

When seen 2 months later, she looked and felt well and had gained 14 pounds. There had been no discharge of placental tissue via the bladder and the discharge from the abdominal sinus was minimal. The mass in the left adnexal region was barely palpable. The patient had menstruated normally for the first time the previous month.

Comment

This patient presented a typical history of secondary abdominal pregnancy. The presence of small bowel obstruction prior to abdominal section and secondary to the incorporation of intestine in the placenta during the

process of placentation is uncommon. The fact that the obstruction was not relieved spontaneously after delivery of the baby and that the placenta remained viable for so long came as a surprise. The failure of placental tissue in this case to degenerate as rapidly as anticipated explains the continuation of the intestinal obstruction. The persistent viability of the placenta could be explained by its extensive attachment and resultant excellent blood supply.

Knowledge gained from this case, will, however, not alter our judgment in the handling of a similar case in the future. We would still elect to deliver the baby as soon as a diagnosis of secondary abdominal pregnancy is established, disregarding fetal age completely. We would do nothing more at the original abdominal section than deliver the baby, provided the intestine was reasonably viable. In the presence of nonviable intestine, we feel that entero-enterostomy (exclusion or sidetracking) would be the procedure of choice rather than an attempt to separate intestine incorporated in placenta.

The fact that an abdominal sinus was still present 6 months after delivery of the baby is not unusual.

The failure of the patient to menstruate until 5 months after delivery, we feel, was based on the continuing production of hormones (probably estrogen) by the residual placental tissue.

The occurrence of an abdominovesical fistula through which the degenerating placenta gained access to the bladder is unusual and interesting. To us, this fact is illustrative of the depth to which syncytial cells will erode in an attempt to acquire an adequate blood supply for the conceptus in a case of secondary abdominal pregnancy.

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A CASE OF INTRA-ABDOMINAL PREGNANCY WITH FOLLOW-UP TESTS FOR DISAPPEARANCE OF PLACENTAL ACTIVITY*

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THE following report presents a case of full-term abdominal pregnancy with a living child, and the mother delivered by laparotomy.

A. P., a 38-year-old Negro primigravida, was admitted to the labor room 2 weeks before her expected date of delivery with mild abdominal pains, crampy in type, and of one week's duration. Her clinic history showed a weight loss of 9 pounds and a persistent positive serologic test for syphilis despite adequate therapy. During the abdominal examination, the small parts were palpated close to the abdominal wall; the breech was at the upper pole; the presenting part was floating and the fetal heart was in the left lower quadrant.

Rectal examination revealed the presenting part at minus 3. There was disagreement between examiners as to the rectal findings, one reporting the cervix not palpable, and the other reporting a palpable cervix admitting a finger tip. Likewise, there was a difference of opinion as to diagnosis, one examiner reporting an intrauterine pregnancy with degenerated fibroid, and the other reporting an intra-abdominal pregnancy.

Sterile vaginal examination disclosed a long, uneffaced, undilated cervix, smaller than would be expected with a full-term pregnancy. The presenting part was not palpated because of extreme tenderness. A flat plate of the abdomen showed a single fetus transversely across the abdomen with marked flexion of the head upon the thorax and with the shoulder presenting. The decision to perform abdominal delivery was based on the transverse presentation in an elderly primipara with no evident progress in labor in the presence of irregular and painful contractions.

Twelve hours after admission, under spinal anesthesia, laparotomy was performed. On visualization of the peritoneum, it was found to be thicker than usual and dark green in color. When it was incised, the amniotic sac was found. The incision was extended, the amniotic sac opened, and the amniotic fluid evacuated. A living female infant weighing 5 pounds was delivered from left occipitotransverse by extension. The body of the infant occupied most of the upper half of the abdominal cavity and part of the lower half. The infant cried spontaneously and respirations were satisfactory. A gentle exploration of the abdomen revealed a single membranous placenta adherent to the left half of the transverse colon, the descending colon, and part of the sigmoid, with some attachments to the small intestine. Exploration of the pelvis showed a uterus in normal position and outline, enlarged to the size of a 6 weeks' gestation, with normal adnexa, all of which were covered with membranes but free of placenta. The placenta was allowed to remain undisturbed and the abdomen was closed in layers with no drainage.

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The postoperative course was normal except for mild distention on the first day. On the ninth postoperative day a small decidual cast was passed per vaginam. The patient left the hospital on the eighteenth day with no complications.

A pregnancy test performed on Oct. 10, 1955, twenty-six days after operation, was still positive. Abdominal examination on Oct. 31, 1955, forty-one days after operation, showed a large, nontender, mobile mass in the left upper and lower abdominal quadrants. Roentgenograms of the abdomen and pelvis showed a homogenous opacity in the abdomen, more marked on the left side. A pregnancy test performed on the fifty-fourth day after delivery showed that no demonstrable chorionic gonadotropin was being elaborated by the placenta.

Comment

This case is illustrative of the typical abdominal pregnancy that has been described by other authors, including the errors in diagnosis. However, pregnancy tests were performed to demonstrate continued functional activity of the placenta which remained in the abdominal cavity. Some time between the twenty-sixth and fifty-fourth postoperative days, the placenta ceased to function. Roentgenograms and abdominal palpation still showed a large, nontender mass in the left upper and lower quadrants at this time.

Summary

1. A case of intra-abdominal term pregnancy with a living mother and child delivered by laparotomy was presented.

2. Pregnancy tests to demonstrate placental activity became negative between the twenty-sixth and fifty-fourth postoperative days.

We wish to thank Dr. William C. Meagher for permission to report this interesting case.

RELAXIN—A CRITICAL EVALUATION*

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AT THE present time the status of relaxin is very controversial and may be likened to that of estrogen and progesterone in the early 1930's. Claims and counterclaims suggest its use for both starting labor and stopping labor. Although our current knowledge is still incomplete, sufficient work has been reported and perhaps unfortunately popularized to warrant a critical evaluation which this report will attempt to present.

Hisaw in the 1920's was impressed by the extraordinary pelvic alteration during pregnancy, particularly the progressive relaxation of the pubic ligaments. He postulated the existence of an unknown ovarian hormone to account for these changes. With no notion of how it worked, or whether it really existed, he named it relaxin. In 1926 he[1] successfully isolated an extract of swine corpora lutea capable of producing relaxation of the pelvic ligaments of the guinea pig. On the basis of his continuing studies as well as those of Kroc and others, physiologists accepted the existence of relaxin and recognized it as a nonsteroid hormone of pregnancy operating interdependently with estrogen and progesterone.

Properties of Relaxin

Pharmacology.—Relaxin is protein in nature but whether simple protein or polypeptide is still undetermined. It is of low molecular weight and is destroyed by the proteolytic enzymes. This latter fact has clinical significance. Relaxin is not available in purified form.

At least three organs—ovary, placenta, and uterus—appear to be involved in the production of relaxin. It is found in the blood and various tissues of the reproductive tract in many mammals during pregnancy. It was first detected in humans by Pommerenke[2] in 1934. In women, the serum concentration increases gradually to a maximum at term and disappears rapidly after delivery. It is of interest to note that relaxin is not found in the serum of men or nonpregnant women. The ovaries of the pregnant sow contain large quantities of relaxin and constitute the chief commercial source at present.

Administration.—Relaxin occupies an intermediate position between rapidly acting hormones such as insulin and oxytocin and more slowly acting ones such as the sex steroids. It is readily absorbed and therapeutic blood levels become available in 3 to 6 hours on clinical dosage. Relaxin is metabolized fairly rapidly and the therapeutic effect begins to decrease in 9 hours and is over in 24

*Presented at a meeting of the New York Obstetrical Society, Dec. 10, 1957.

hours. It may be administered either intramuscularly or intravenously. Oral administration is controversial because of the previously mentioned protein nature and the probable destruction by proteolytic enzymes.

Toxicity.—There seems to be general agreement that relaxin is nontoxic and relatively free of adverse effects.[3, 4] Pain at the local site may occur following intramuscular administration. Antigenicity has not been a problem in spite of the protein nature of this substance.

Standardization.—The action of relaxin on the symphysis pubis of the guinea pig is rapid and constant and this serves as a basis for bioassay and standardization. Originally standardization was in terms of guinea pig units, 1 guinea pig unit being the amount necessary to induce relaxation of the symphysis pubis in estrogen-primed castrated guinea pigs. The relaxin now available for clinical use is standardized in terms of milligrams of a relaxin standard. One milligram equals 150 guinea pig units. Relaxin is now available as Releasin* and Cervilaxin,† both preparations containing 20 mg. per cubic centimeter.

Physiologic Action.—The physiologic actions of relaxin have been sufficiently established to form a sound basis for clinical application. They consist chiefly of: (1) relaxation of the pelvic joints; (2) softening of the cervix; and (3) initiation of labor in the laboratory animal. For relaxin to be effective the connective tissue of the pelvic joints must first be primed by estrogen.[5] The process of joint relaxation and softening begins with dilatation of the blood vessels and is followed by absorption of fluid, alteration of the ground substances, and dissolution and splitting of collagenous fibers. This occurs within 6 hours of the injection of relaxin and although a similar alteration may be brought about by steroid hormones a significantly longer time is required.

Relaxin administered to stilbestrol-primed castrated sows and heifers results in cervical dilatation, whereas estrogen alone does not have this effect.[6, 7] The cervix of the untreated animal cannot be dilated.

In prepubertal mice in which ovulation and pregnancy were induced and maintained with exogenous hormones, administration of relaxin resulted in opening of the birth canal and initiation of labor. It is possible that relaxin may have caused a release of oxytocin to produce uterine contractions. Kroc,[20] experimenting with pregnant ovariectomized mice, noticed that progesterone inhibited the action of relaxin and felt that induction of effective labor was dependent upon a progesterone-relaxin balance. The work of Boucek and associates[8] demonstrated that relaxin reverses the aging processes in connective tissue and inhibits cholesterol synthesis of connective tissue cells.

Clinical Applications.—On the basis of the experimental and animal work that has been done, many investigators have studied the effect of this hormone on dysmenorrhea, inhibition of uterine contractions, softening of the cervix, and collagen diseases. Unfortunately, reports of these clinical studies in humans have often been conflicting or confusing. First reports were concerned with the use of relaxin in the treatment of premature labor. Abramson and Reid[9] in a preliminary study reported successfully arresting premature labor in 5 patients who were given intramuscular relaxin. These pregnancies continued to term with the birth of a normal infant in each case.

Folsome and his co-workers[10] reported favorable results in a group of 40 patients in premature labor treated with relaxin. The fetal salvage rate was 71 per cent and complete arrest of premature labor was obtained in 57.7 per cent of the patients. More recently McCarthy, Erving, and Laufe,[11] using

*Warner-Chilcott Laboratories.
†The National Drug Company.

relaxin to treat threatened premature labor, concluded that relaxin did inhibit premature contractions in "uncomplicated" cases of premature labor. They were of the opinion that it was of little use if the membranes were ruptured. Paradoxically it has also been reported from these and other series that in many cases, rather than stopping labor, the use of relaxin was followed by rapid cervical dilatation and prompt delivery.[10, 12] Eichner[12] used relaxin in patients about to undergo a therapeutic abortion. It was his impression that the cervix was softer, and that the drug contributed to the ease of cervical dilatation and evacuation of the products of conception.

Maclure[13] reported on the use of relaxin to assist in the induction of labor in a series of 15 cases of retained dead fetus. Success was achieved in 11 of these cases. Recently, Birnberg and Abitbol[14] claimed that the use of relaxin at term softens the cervix and shortens labor by one half to two thirds in selected patients.

In an attempt at a more objective evaluation of the effect of relaxin on the uterus, Kelly and Posse[15] made tokodynamometric studies in 25 patients, using the intrauterine electrodes of Karlsen. They were unable to demonstrate any inhibition of uterine contractions.

Current Studies.—In our own institution, the studies started by Dr. Folsome on the use of relaxin in premature labor were continued for approximately one year. In a series of 72 patients, the results were poor and no better than might be expected on the basis of pure chance. For this reason the protocol sheets of the cases previously reported from our institution were carefully reanalyzed. This brought out clearly that the apparent effectiveness of relaxin was present only in patients who had minimal dilatation and effacement with intact membranes. In patients who were definitely in labor as evidenced by dilatation and effacement or rupture of the membranes, we were unable to stop uterine contractions and apparently only succeeded in accelerating labor and delivery in many cases.

The Present Study

On the basis of these observations, the reports cited above, and more importantly the accepted physiologic actions of relaxin, it seemed warranted to study its effect on the term cervix.

Material and Method.—To date the series includes 97 pregnant women at or near term in whom indicated or elective induction of labor was contemplated. The only criterion for selection was the condition of the cervix. Each patient had an unripe, unfavorable cervix of firm consistency, without effacement or dilatation, and in the posterior location. All patients were examined by the same investigator in order to rule out differences in the interpretation of the status of the cervix.

Dosage.—The patients received 2 c.c. (40 mg.) of relaxin* intramuscularly on the evening prior to induction. On the following morning 6 c.c. in 500 c.c. of 5 per cent dextrose in water was administered by continuous intravenous drip. The rate of infusion was 60 drops per minute. Two hours after completion of the relaxin infusion, intravenous oxytocin drip was started according to the technique previously described.[16]

Controls.—In order to obtain some degree of control, patients who went into labor spontaneously or whose membranes ruptured spontaneously were

*Clinical supplies of this material under the trade name Releasin were furnished by Warner-Chilcott Laboratories.

excluded from the study. No amniotomy was performed as part of the induction technique. Further control was achieved by giving other patients selected according to the same criterion of cervical status a placebo instead of relaxin and then following it with oxytocin according to the plan outlined above.

Results.—If labor did not result and delivery did not follow this regime, the case was considered a failure. We have been encouraged by our results to date (Table I). Sixty-two patients received relaxin and oxytocin and 35 patients received a placebo and oxytocin. Of the relaxin-treated patients, labor was successfully induced in 43, or 71.5 per cent. In 19 cases, 28.5 per cent, the attempt at induction failed. In a control group, labor was successfully induced in only 8 patients, 22.8 per cent, and there were 27 failures, 77.2 per cent.

TABLE I. RESULTS IN INDUCTION OF LABOR

	SUCCESSFUL		UNSUCCESSFUL		
	NO.	%	NO.	%	TOTAL
Relaxin	43	71.5	19	28.5	62
Placebo	8	22.8	27	77.2	35

Softening of the cervix as determined on vaginal examination was a fairly constant finding in all patients treated with relaxin. This does not mean that there was increased effacement or dilatation prior to the use of oxytocin. The effect of relaxin on the cervix was not clinically demonstrable in less than 3 hours after its administration. In a few cases where the routine could not be carried out after the relaxin had been administered, we had the opportunity of observing the transient nature of the relaxin effect. The cervix became soft but on re-examination the next morning it had again become firm and reverted to its original condition.

In 4 additional cases the relaxin-oxytocin combination was used because of retention of a dead fetus. Induction was successful in all 4 cases. One case is of particular interest:

E. S., a 36-year-old gravida iv, para iii, was admitted on September 5 because of the cessation of fetal movements and "something in the vagina." The estimated date of confinement was Dec. 31, 1957. Her prenatal course was marked by repeated episodes of bleeding. Examination disclosed a pregnancy of 5 months' duration; no fetal heart beat was heard and the cord was found prolapsed through an undilated rigid cervix. Oxytocin induction was attempted but was unsuccessful. The relaxin-oxytocin combination was used and resulted in noticeable softening of the cervix and eventual delivery of a stillborn premature infant in breech presentation 6 hours after the start of the relaxin infusion.

Reactions.—Very little untoward reaction to the drug was noted. One patient developed an urticarial type of rash which responded promptly to antihistaminics. Two patients had chills suggesting a pyrogenic reaction. There were no adverse effects on blood pressure, pulse, temperature, or blood count. Relaxin is apparently compatible with other drugs, including oxytocin, analgesics, and anesthetics.

Comment

There is little doubt that relaxin exists. There is also little doubt that it has biologic activity. Here, however, the positive statements must end. Its use to treat premature labor is, to us, illogical on the basis of its physiologic

activity in animals and the results reported even by those who advocate such use. Premature labor is a nebulous condition; most studies report 60 per cent of the cases showing no specific etiological factor. The other 40 per cent may be due to varying obstetric and medical conditions, many of which would not be amenable to relaxin therapy even if relaxin did all that has been claimed for it. Obviously relaxin would not be indicated and might even be harmful in the case of premature labor associated with abruptio placentae.

To credit any agent with the ability to stop labor, one must be sure that the patients were actually in true labor. The status and progress of the labor when the drug was started must also be known. In many cases of reported success, the patients were probably not in either true or advanced labor.

Relaxin will soften the cervix. We are convinced of this clinically and are using special biopsy techniques with histochemical staining in an attempt to prove this objectively. This observation is supported by the animal work and physiologic activity previously cited. It does not imply, however, that relaxin dilates the cervix or initiates labor in humans. Oxytocin either endogenous or exogenous is still necessary to produce effective uterine contractions.

On the basis of the softening effect, we feel that relaxin offers a safe adjunct to the medical induction of labor when indicated. In a number of our cases its use made delivery possible without cesarean section or repeated oxytocin stimulation to overcome an unfavorable cervix. The success obtained in the treatment of patients with fetal death prior to the onset of labor appears especially valuable. It is generally agreed that conservative management and a hands-off policy are preferred in these cases.[17] Undoubtedly this concept resulted to some degree from a lack of a satisfactory method of emptying the uterus. In view of the possibilities of hypofibrinogenemia and the dangers from psychic trauma that may be present in the patient with a retained dead fetus, it is often necessary to make some attempt to empty the uterus. The combination of relaxin and oxytocin appears to offer an effective procedure to achieve this end.

We have had no results indicating that labors were shorter when relaxin was used. Recent reports of high success in shortening labor were in patients who received supplemental oxytocin in the presence of advanced cervical dilatation and effacement and ruptured membranes. Patients with these findings offer no criteria for evaluation of the drug since they are already in active labor. It is suggested that the short labor in these patients can be attributed to the action of oxytocin alone when used under ideal conditions.[18]

The optimum dosage is still to be arrived at. Indications at present are that less than 80 to 120 mg. will prove to be ineffective in softening the cervix. With adequate dosage all patients will respond with softening of the cervix. It was unusual to see a response before 2 hours and so any results which occur within an hour can hardly be attributed to the effects of relaxin.

We are fully aware of the shortcomings of a study such as ours in which the action of a drug is evaluated according to crude clinical methods. The investigation would be more meaningful if the clinical evidence could be paralleled by objective laboratory evidence. This would include biopsies of the cervix for special histochemical stain and analysis and assays of the blood level in humans. At present we are carrying out tests on cervical biopsies and hope to report results of histochemical analyses very shortly. Determinations of blood levels in the human would be most valuable but present methods necessitate 500 c.c. of blood and the accuracy of such testing is still questioned by some authorities.[19, 20]

By continuing these studies and enlarging the clinical series, by proceeding with cervical biopsies and with help from the research workers in this field, we hope to arrive finally at a true evaluation of the place of relaxin in obstetrics.

Conclusions

1. The exact place of relaxin in the treatment of premature labor is uncertain. Although some success has been reported, it has been of little value in our studies.

2. Relaxin does soften the cervix of pregnant women and thus it appears to be a worthwhile adjunct to the medical induction of labor. In a series of 62 patients treated with relaxin and oxytocin, successful induction was obtained in 71.5 per cent. In a control group of 35 patients who received a placebo and oxytocin, the success rate was 22.8 per cent. Both groups were selected on the basis of an unfavorable cervix.

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Discussion

DR. DUNCAN E. REID.—Currently uterine motility is being intensively studied; and patterns of uterine contractions in normal and abnormal pregnancy and labor have been recorded. Considerable effort has been made to elucidate the effect of various substances on myometrial activity. The significance of progesterone, long regarded as the hormone responsible for uterine inactivation, has been re-emphasized by Corner and Csapo[2] in their "progesterone block" theory. In accordance with the observations of Horvath,[4] the intracellular K:Na ratio of the myometrium is decreased under progesterone, and this relative increase in intracellular sodium and loss of potassium favor a quiescent muscle. Thus, uterine motility will depend upon whether the myometrium is under estrogen or progesterone domination.

It is now appreciated that the cervix has a role to play in maintaining pregnancy, and premature parturition, as well as successful parturition, may be due to changes in the cellular elements of the cervix, changes which may precede actual mechanical dilatation. Dr. Stone suggests that relaxin may play a role in causing changes in the cervix, and he makes reference to its therapeutic use in parturition in some farm animals. That relaxin should alter the cervix would not be surprising, for its chief effect is apparently on connective tissue. Since Danforth's observations, it is appreciated that the cervix is composed mostly of connective tissue, and that it is not a sphincter either morphologically or physiologically. It seems evident that the control of pregnancy and parturition cannot be assigned to a single cause.

Dr. Stone calls attention to the earlier clinical trials of relaxin, when it was advocated in the treatment of repetitive or habitual premature labor.[1] In these cases, it is difficult to determine the therapeutic response to any substance, for, as Dr. Stone has said, there is no sure way of telling whether a patient having uterine contractions is in labor until the cervix begins either to be effaced or to dilate. Even with the methods currently used to record uterine motility, it is difficult to differentiate between true and false labor. It is generally conceded that when the cervix begins to dilate, the uterus will not retain the conceptus by endocrine therapy alone, whether it be progesterone or relaxin, alone or in combination. This hardly allows the conclusion, however, that in the course of normal pregnancy relaxin may not influence uterine motility. Before discarding the possibility that relaxin may have a paradoxical action in that it may inhibit the myometrium and also cause the cervix to dilate, it is perhaps well to be reminded that epinephrine also has a paradoxical action on the myometrium, depending upon the amount administered. The place of relaxin in the reproductive process remains uncertain. In retrospect, perhaps relaxin might accelerate premature delivery if given after labor is established. In point of fact, all forms of endocrine therapy in repetitive premature labor, including diethylstilbestrol and progesterone in physiologic doses (200 to 300 mg. per 24 hours), have been disappointing. Clinicians are well aware that in many of the patients with repetitive premature labor the cervix dilates without apparent discomfort and in the presence of a relatively quiescent uterus. This suggests that the cervix in these cases is either prepared prematurely for labor or that it is anatomically incompetent, as suggested by Lash and others. The current universal interest in the latter possibility suggests that the treatment of patients with diethylstilbestrol and progesterone, alone or in combination, is not enough, and a mechanical factor may be involved. If surgical treatment of cervical incompetence has validity and proves valuable in the proper cases, i.e., those with repeated reproductive failures due to premature labor, this adds further evidence for the belief that the cervix, too, must perform according to a normal pattern in the course of normal pregnancy and parturition.

Rather than any special action on the myometrium, as has been suggested, relaxin may be present for the purpose of preparing the birth canal for labor. Realizing that it is a minority opinion, I believe that uterine inertia may arise from cervical resistance or dystocia, similar to its frequent occurrence in cases of bony dystocia. This is supported by the clinical observation that prolonged labor, the result of ineffective uterine contractions or uterine inertia, is a syndrome of the primipara or of first labors. This suggests that the cervix, once having dilated completely, is suitably prepared for subsequent labors. As Dr. Stone's paper suggests, perhaps it is here that relaxin may have its greatest therapeutic usefulness. Certainly this would be a distinct advance if it were possible to prevent prolonged labor with its attending fetal morbidity and mortality.

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DR. R. GORDON DOUGLAS.—Our own experiences are in agreement with Dr. Stone's in that we were disappointed in not being able to prevent the progression of premature labor. These results were not in conformity with the early reports indicating considerable success along these lines.

I was much interested to hear Dr. Stone's discussion of dysmenorrhea and the somewhat paradoxical situation of the use of this hormone as a possible aid in the induction of labor. I think Dr. Reid has referred to a number of very fundamental concepts. He referred to the work of Drs. Corner and Csapo. The latter is firmly convinced there is a higher concentration of progesterone or related substances situated in the area of the uterus adjacent to the placenta. The concept of a disturbance or the alteration in the electrolytes that is responsible for the initiation of labor contractions is intriguing. Dr. Csapo has an explanation for the fact that exogenous progesterone does not always work in clinical practice. According to him it takes a period of time for the progesterone to break down before it is effective in the prevention of uterine contractions. This time factor has been calculated as approximately 19 hours.

Both speakers referred to oxytocin and yet no mention was made of vasopressin. In the chemically pure or synthetic form we believe this drug is a most potent agent in effecting contraction of the uterus in the nonpregnant state and during early pregnancy. This action apparently is reduced during pregnancy and at the same time there is an ascendency in the ability of oxytocin to contract the uterus as pregnancy progresses. Additional experimental work in these areas is indicated.

DR. CARL T. JAVERT.—There is a study of Releasin going on at Woman's Hospital at the present time; so far, 25 patients have been treated with Releasin and there were 25 control cases. The primary purpose of the study is to evaluate the effects of this hormone upon the cervix at term. The 25 patients given Releasin and the 25 control patients had normal pelves and a normal antepartum course. There was no demonstrable effect in the Releasin-treated group as compared with the control. As a matter of fact, we did find, according to Dr. James Ko, who is conducting this investigation, that Releasin seems to prolong labor rather than shorten it. He has been called upon 6 times to use Pitocin in order to effect ultimate delivery in the 25 treated patients. So at the moment we are in a dilemma as to the efficacy of this drug in hastening parturition or delivery in normal patients. On the other hand, we feel that this drug has a salutary effect in slowing down the uterine contractions and have gone so far as to consider Releasin as a uterine tranquilizer, or a uterine anodyne.

DR. GORDON W. DOUGLAS.—At Bellevue Hospital Dr. Wayne Decker has been studying the use of this compound in obstetrics for about 2 years in patients with premature labor, in patients with uterine inertia, in a small group of patients to determine the effect on the cervix, and in a somewhat larger series of patients with toxemia of pregnancy. He is preparing these results for publication.

There were two series of patients with premature labor. One was given nothing and the other was given what were considered to be therapeutic doses of Releasin. In the control group, slightly over 30 cases, all but one patient in premature labor proceeded to delivery. Of the slightly over 30 patients given Releasin, all but 3 proceeded rapidly to delivery. The study was concluded at that point.

DR. ALAN F. GUTTMACHER.—We tried Releasin in premature labor with about the same success Dr. Douglas reports.

I would be curious to know whether Dr. Reid or Dr. Stone has had any results with Releasin in cervical dystocia. Dr. Reid stated it was more common than uterine inertia. We sorely need a drug which would aid in the spontaneous dilatation of the leathery, 4 cm. cervix which stands still, as well as the cervix which gets increasingly edematous as unsatisfactory labor continues.

DR. STONE (Closing).—Both Dr. Reid and Dr. Douglas made the essential point that the hormonal picture affecting the gravid uterus may involve several different factors at varying stages of a pregnancy. What happens in cases of premature labor may not be what happens at term. The levels of estrogen and progesterone are involved along with the levels of relaxin. The interrelationships of all three hormones are most important. The question of dosage is also very significant. It has been suggested by other investigators that better results might obtain with larger dosages. At present, a consensus of most relaxin studies done in this city would be that our success in stopping premature labor has not been very great.

I was glad to hear the comments on dysmenorrhea. We have not used relaxin for this condition, nor are we impressed by the reports in the literature. To date we have not used oral relaxin for any condition.

In reference to Dr. Javert's comments, I would like to emphasize the first point made. We do not believe relaxin shortens labor. Oxytocin, natural or administered, must be present to cause contractions. We do feel that relaxin will soften the cervix, Dr. Guttmacher. We have not used it in cases of prolonged labor with cervical dystocia, but rather to induce labor in patients with an unripe cervix.

Just before leaving the hospital this evening, I received the reports on the first two biopsies which I referred to and which are being subjected to special histochemical analysis. These biopsies are taken with the Silverman needle to get stroma rather than mucosa alone. They were taken on the same patients before and after administration of relaxin. In the two reported on at present there was no demonstrable change or evidence of relaxin effect. Of course, many more biopsies will be needed before conclusions can be drawn.

THE INTRAUTERINE BOUGIE AND VOORHEES BAG TODAY

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IN THIS day of modern obstetrical practice the older methods of induction of labor tend to be neglected and forgotten. It is our purpose to review all the cases at the E. J. Meyer Memorial Hospital from Jan. 1, 1943, until June 30, 1957, and from the Sisters of Charity Hospital from Jan. 1, 1951, until June 30, 1957, in which a bougie or bag was used either in the induction of labor or in the management of placenta previa.

During this period a bougie or bag was used in 78 instances in 37,998 deliveries. This very infrequent use of the bougie and bag is significant in itself—demonstrating the general feeling that there are now more efficient, safe, and satisfactory methods of inducing labor and managing placenta previa. The question arises: Is there still a place for the bougie and bag today?

Techniques of Insertion

For the insertion of either bougie or bag, the patient is placed in the lithotomy position and prepared as for delivery. As a rule no anesthesia is required when a bougie is inserted.

The bougie used in this series was an ordinary long, thick-walled sterile rectal tube. In one case two catheters were used instead. It is inserted through a speculum or by the sense of touch directing the tip extraovularly and, with a twisting motion, feeding the remainder of it into the lower uterine segment by means of a ring forceps so that the entire bougie is coiled in the lower uterine segment. The vagina is then packed with sterile gauze to keep it in place.

Other types of bougies were once in common use. Among these are the Wales bougie, the Krause bougie, various stomach tubes, and animal bladders.

During the introduction of the Voorhees bag the patient may, and frequently does, require an anesthetic, but this is given only if painful manipulations are anticipated or initiated. In our series the largest bag possible was used—in most cases a size 5 or 6. The sterile bag is lubricated, folded as small as possible, grasped with a ring forceps, and introduced through a bivalve speculum through a cervix which is 1 to 3 fingers dilated, soft, and at least 50 per cent effaced.

In cases of placenta previa the membranes must be ruptured during the procedure or further separation of the placenta can be expected. Otherwise the membranes are left unruptured if possible, but this factor is not a major consideration. The bag is then filled with sterile water and connected to a weight—usually 1 pound—which hangs over the end of the bed or delivery table.

The Bougie

The bougie was used in 39 cases with success in 31 instances. A factor which must be kept in mind is the frequent use of other methods of induction prior to, in conjunction with, or following insertion of the bougie. This may cloud the results as to the efficacy of the bougie itself. Table I shows the other methods of induction, the numbers referring to the number of inductions attempted.

TABLE I. RELATIVE EFFECTIVENESS OF BOUGIE COMPARED WITH RESULTS OF OTHER INDUCTIONS

OTHER TYPES OF INDUCTION (NO. OF INDUCTIONS)	PRIOR TO BOUGIE (FAILED)	WITH BOUGIE (SUCCESS)	AFTER BOUGIE	
			(SUCCESS)	(FAILED)
Calgluquine* and Pitocin	14	6	3	
Intranasal Pitocin		4		
Intravenous Pitocin drip	10	5	1	3
Rupture of membranes		1		

*Calcium gluconogalactogluconate plus quinine gluconate, Sandoz Chemical Works, Inc., New York, New York.

It need hardly be said that in cases in which success is reported with other methods used in conjunction with the bougie we cannot be definite in stating which mode of induction was the more efficacious or whether both played a part.

There were 9 cases in which the bougie alone was used. In 8 of these cases after labor was initiated the total labor did not exceed 11 hours, the average being 8.5 hours. In one case the bougie was left in the uterus 50 hours. The patient had severe pre-eclampsia with hypertensive cardiovascular disease and was in congestive heart failure. She was in an oxygen tent during the induction and spontaneously delivered a 2 pound, 6 ounce stillborn infant 5 minutes after the bougie was removed. In the majority of cases the bougie was left in the uterus between 7 and 22 hours, the shortest time being 4 hours and the longest 50 hours.

In Morton's[1] series of 160 bougie inductions labor was initiated within one hour after the insertion of the bougie in 14 per cent of cases, the average interval between insertion of the bougie and the onset of labor being 6.4 hours.

Indications.—The most common indication for induction with the bougie was pre-eclampsia. Failure of other methods of induction was the next most common indication in our series. Eclampsia, hypertensive cardiovascular disease, dead fetus, chronic renal disease, rheumatic heart disease, hydramnios, diabetes mellitus, uremia, and rising Rh titer were further indications. Other series give as indications tuberculosis, unstable presentation, previous cesarean section, minor degrees of contracted pelvis, and postmaturity.

Table II shows the successes, failures, and fetal mortality.

TABLE II. CLINICAL RESULTS IN CASES TREATED BY BOUGIE

TOTAL SUCCESSES WITH BOUGIE	FAILURES	FETAL DEATHS ATTRIBUTABLE TO BOUGIE	STILLBIRTHS	NEONATAL DEATHS	CORRECTED FETAL MORTALITY	LIVING INFANTS
31 (79.5%)	8 (20.5%)	0	10 (25.6%)	6 (15.4%)	0	23 (59%)

The success rate is impressive enough to warrant notice, particularly in view of the fact that it succeeded in 8 of 9 patients who had previously not responded to medical induction.

The number of stillbirths and neonatal deaths makes one suspicious. In these cases induction of labor was deemed imperative enough for the lack of maturity of the fetus to be ignored. All of the 16 fetal deaths were in the group in which the mother had severe pre-eclampsia or eclampsia or in cases where the fetus was known or presumed to be dead. All but one of the deaths occurred in premature or immature fetuses. Five of the stillborn infants were presumed dead prior to induction.

Morton[1] reported an 82 per cent success rate using the bougie. Knerr[5] reported up to 98.5 per cent success. A gross fetal mortality rate of 18 per cent[1] with a rate of 3 per cent fetal deaths caused by the procedure is more encouraging than our 41 per cent gross fetal mortality, but at the same time leaves much to be desired.

Morbidity.—Three of the 39 patients became morbid. In 12 instances the bougie was left in the uterus 24 hours or longer. No one in this group became morbid although 5 patients did receive penicillin prophylactically.

Maternal Mortality.—Two patients died, one in eclampsia, the other in terminal renal failure. The bougie was blameless in both cases.

Complications.—No serious complications arose such as severe hemorrhage or rupture of the uterus. In one case a bougie was inserted, moderate bleeding ensued immediately, the bougie was promptly withdrawn, and the bleeding ceased. Blood loss in these cases did not exceed that expected for ordinary deliveries.

Comment.—Certain disadvantages and dangers of induction by means of the bougie are not to be ignored. Displacement of the presenting part causing prolapse of the umbilical cord or difficult delivery is a serious complication. Sepsis, another danger, is fairly readily controlled in this antibiotic era. Undermining of the placental site with severe hemorrhage is sometimes encountered.

Eastman[2] stated that bougie induction has a definite field of usefulness in cases in which rupture of the membranes is contraindicated, i.e., cases in which delivery is fairly urgent, particularly 3 to 4 weeks from term, and the cervix is long and partially closed.

The Voorhees Bag

The Voorhees bag was used in 39 cases with success in 38 of these. In 13 cases medical induction (either intravenous Pitocin drip or intramuscular Pitocin) was instituted at the time of insertion of the bag.

Indications.—The bag was used in 21 cases in which various degrees of placenta previa were diagnosed under sterile conditions in the delivery room. Other indications were prolapsed cord, dead fetus, transverse lie with ruptured membranes, abruptio placentae, hydrocephalus, intrapartum infection with ruptured membranes, and face presentation.

TABLE III. CLINICAL RESULTS IN CASES TREATED WITH VOORHEES BAG

TOTAL SUCCESSES WITH BAG	FAILURES	FETAL DEATHS ATTRIBUTABLE TO BAG	STILLBIRTHS	NEONATAL DEATHS	CORRECTED FETAL MORTALITY	LIVING INFANTS
38 (97.4%)	1 (2.6%)*	1 (2.6%)	20 (51.3%)	6 (15.4%)	7 (18%)	13 (33.3%)

*A No. 3 bag fell out in 20 minutes.

Table III shows the percentage of successful inductions with the use of the Voorhees bag. One naturally questions the use of a bag in the face of such

an alarmingly high fetal mortality rate. Of the 20 term fetuses in the series in which the bag was used 10 were stillborn. Five of these were apparently normal at birth and might have been saved had a cesarean section been performed soon after admission. The indications for use of the bag in these cases was either placenta previa or transverse lie. In the successful cases the bag was left inside the uterus between a half hour and 27 hours, the average duration being 4.5 hours. After expulsion or removal, delivery usually followed within a few minutes; in only 4 instances did more than an hour elapse.

In Morton's series of 49 inductions success was reported in 93.8 per cent. His series did not include placenta previa or abruptio placenta as indications. The gross fetal mortality rate in his series was 47 per cent. He reported an incidence of prolapsed cord of 17.4 per cent with 75 per cent of these infants subsequently stillborn.

Waters[3] felt that the most valuable sizes of bags are the Nos. 4 and 5. Morton used the largest bag possible. Other authors[6, 10] felt that the use of a bag larger than a No. 3 or 4 is attended by a relatively high degree of cervical and perineal lacerations. Except in cases of placenta previa in which the largest bag possible is used for the tampon effect, these authors felt that a No. 3 or 4 is entirely satisfactory.

The necessity of performing a vaginal examination to rule out prolapsed cord or change of presentation was emphasized by Waters.[3] He found in a series of 372 bag inductions that these 2 complications were the most frequent causes of stillbirths. Other dangers attending the use of the bag were prolapse of an arm, infection, lacerations of the cervix, and hemorrhage.

Houston[6] showed in a series of 226 cases between 1926 and 1938 that about 18 per cent failed to have sufficient dilatation of the cervix for success to be attributed to the bag.

The gross fetal mortality in Houston's series was 59 per cent, the corrected figure being 25 per cent. Maternal morbidity in this same series was 30 per cent and the maternal mortality was 8 per cent.

Morbidity.—This was not a problem in our series. Antibiotics was used rarely and there was only one case of morbidity.

Methods of Delivery.—Version and extraction were used 24 times, and breech extraction 4 times. There were 10 vertex presentations and one face presentation.

The high incidence of internal podalic version and extraction of the fetus is necessitated by the displacement of the presenting part—usually the head—by the bag, requiring the more hazardous mode of delivery when the cervix attains full dilatation.

Blood Loss.—Blood loss was estimated after the initial loss in cases of placenta previa. The average was approximately 1,000 c.c., the range being 600 to 2,500 c.c. Rupture of the membranes with insertion of a large bag is an excellent hemostatic device.

Comment.—The success of the Voorhees bag in this series was excellent with respect to induction (97.4 per cent). The fetal salvage, however, was only 33.3 per cent. It appears that this method of induction and of controlling hemorrhage from placenta previa does not favor a high fetal survival rate.

In a series of 200 cases of placenta previa Grant[11] quoted a cesarean section rate of 76 per cent. The gross fetal mortality in this group was only 11.9 per cent of 201 fetuses. Seventy-five (37.5 per cent) of these patients were treated expectantly (hospitalization, bed rest, careful observation, blood on reserve at all times) for periods of from 2 to 10 weeks to allow the fetus to attain

greater maturity. Fetal loss in this conservatively treated group was 16 per cent, which is far more encouraging than our 67 per cent with the Voorhees bag. In Grant's series no Voorhees bags at all were used. Willett's forceps were used in 3 cases and artificial rupture of the membranes was used next in frequency to cesarean section.

Conclusions

1. There is still a limited field of usefulness for the bougie and bag in today's practice of obstetrics.

2. The bougie and bag carry little hazard to the mother if ordinary care is taken.

3. Conservatism, expectation, and the liberal use of cesarean section in cases of placenta previa carry a favorable prognosis for the fetus without jeopardizing the safety of the mother. On the other hand, use of the Voorhees bag is attended by a high fetal mortality.

4. In cases of known or presumed dead fetus in which early delivery is indicated, a bougie or bag is usually effective and may obviate the necessity for cesarean section.

5. In selected cases in which delivery is imperative (particularly cases of pre-eclampsia) but in which medical induction and/or rupture of the membranes is unwise, unfeasible, or unsuccessful, the introduction of a bougie is usually rewarded with success.

Thanks are due Dr. Edward G. Winkler for his helpful suggestions in the final preparation of this manuscript.

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THE CASE OF THE MISSING CATHETER

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MANY cases of perforation of the uterus resulting from an attempt to produce abortion have been reported. When the instruments are introduced into the uterus and it is perforated, abortion usually results,[1] but occasionally pregnancy may continue to term.

In a review of the literature, only 2 cases have been reported wherein the uterus had been perforated by a catheter, the catheter was removed surgically from the abdomen, and the patient subsequently was delivered of a living healthy infant.

Bateman[2] reported a case of perforation by a catheter at 3 months' gestation. The catheter was removed from the peritoneal cavity and adhesions between the site of perforation on the posterior uterus and the sigmoid were not disturbed. The pregnancy continued to term and was terminated by low cervical cesarean section because of pre-eclampsia and the uncertainty as to the behavior of the adhesions between the sigmoid and the uterus during labor. Cohen and Fleischer[3] reported a case at 6 weeks' gestation in which one end of the catheter projected through the perforation on the anterior surface of the uterus and lay free in the peritoneal cavity. The catheter was removed and the pregnancy continued to term.

The following case is one similar to those reported:

A 24-year-old unmarried gravida i, para 0, white woman was first seen in the emergency room at Baylor University Hospital, May 5, 1957, at 4:55 A.M. with the complaint of excruciating lower abdominal pain for one week.

Five weeks previously a catheter had been inserted into the uterus and the vagina filled with a pack. Within a few hours she experienced a mild cramping sensation. Twenty-four hours later the patient removed the catheter and pack as she had been instructed. Following this, she again experienced mild cramping for one day and a few episodes of vaginal spotting. Three weeks later, on April 26, another attempt was made to produce abortion in the same manner as outlined above. On the following day, however, when the pack was removed, the catheter could not be found. During the following week the patient experienced considerable intermittent cramping in the lower abdomen and a slight amount of vaginal bleeding. Approximately 14 hours prior to admission to the hospital a third attempt was made to insert an instrument into the uterus. Following this, the patient experienced severe lower abdominal pain.

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The patient's temperature was 99.6° F., pulse 120 per minute, and respirations 28 per minute, respectively, and her blood pressure was 126/69. The patient was slender, appeared pale, apprehensive, and acutely ill. She was, however, alert and cooperative.

Examination disclosed an extremely tender, distended abdomen and rebound tenderness below the umbillicus.

On pelvic examination a copious sanguineopurulent discharge oozed from a severely traumatized cervix. The uterus was the size of a 12 to 16 weeks' pregnancy. A bimanual examination could not be performed adequately. A diagnosis of an infected, induced, incomplete abortion, with septicemia and peritonitis, was made.

Fig. 1.—The coiled catheter lying free in the pelvic cavity is indicated by the cross marks.

A culture of the vaginal discharge, a blood culture, analysis of a catheterized urine specimen, hemoglobin determination, leukocyte count, and differential examination were made immediately. The vaginal culture revealed *Escherichia coli*, *Aerobacter aerogenes*, and anhemolytic streptococci. The blood culture showed no growth after 10 days. The white cell count was 21,000 with 20 band forms, 73 segmented cells, 6 lymphocytes, and 1 mononuclear leukocyte. The hemoglobin was 11.5 Gm. X-ray examination of the abdomen showed a catheter lying free in the abdominal cavity and an early ileus (Fig. 1).

Intravenous Chloromycetin, 1 Gm., Demerol, 100 mg., and tetanus antitoxin, 10,000 units, were administered immediately. Ten million units of penicillin and 1,000 c.c. of compatible blood were given prior to operation.

On May 5, 1957, abdominal operation was performed. A No. 16 French catheter lying free in the abdomen was removed. There was no free blood in the abdomen and after

a superficial and unsuccessful exploration for the point of perforation in the uterus, the abdomen was closed. It was felt that an unnecessary amount of handling of an infected, pregnant uterus was unwise at this time.

The patient had an uneventful recovery and was discharged from the hospital May 10, 1957, 5 days after operation. From this point the pregnancy progressed without incident.

On Oct. 26, 1957, the patient was again admitted to Baylor University Hospital in labor at term. After 12 hours of uncomplicated labor, a normal 7 pound, 3 ounce living male infant was delivered per vaginam with the aid of low forceps. The patient was discharged from the hospital 4 days after delivery with no complications.

She had been married in the meantime and was very happy about carrying her baby to term.

Comment

In retrospect, the instrumentation in this case was probably done with a wire director attached to the catheter, although it is possible for a soft catheter to be pushed through the wall of a uterus, especially if infection is present.

Careful examination of the vaginal fornices showed no evidence of perforation. This, with the traumatized, infected cervix, led to the conclusion that the catheter must have entered the uterus at the time of instrumentation.

It is probable that the opening, which had been made 9 days previously and which was probably small, had healed by the time of the abdominal operation.

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REMOVAL FROM THE PARAMETRIUM OF A NAIL EMPLOYED TO INDUCE ABORTION

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THE subject of foreign bodies in the pelvis after attempted abortion was very well covered in a recent article.[1] The great diversity of metallic and nonmetallic objects found was noted, "limited only by their availability and by the patient's imagination as well as, perhaps, her state of desperation."

Another paper in a facetious vein reported a number of unusual foreign bodies found by gynecologists.[2] In neither review were nails mentioned. We are now presenting such a case.

S. R., a 28-year-old woman, para i, gravida i, was transferred to Harlem Hospital on May 17, 1957, from another hospital where she had been for the previous 5 days. She had been admitted to the first hospital because of lower abdominal pains with a diagnosis of threatened abortion. She denied missing any periods, her last one being around April 25, for four days. During her stay in the first hospital, she became febrile. An x-ray of the abdomen was taken on the third day there, and showed a nail in the pelvis. She was re-examined then and was told that the nail could be felt vaginally. She was given antibiotic therapy, but after 2 more days she had herself transferred to our institution, presumably because she was dissatisfied with the therapy.

At the time of her admission to Harlem Hospital, her temperature was 101.6° F., pulse 92 per minute, and the blood pressure 110/70. The abdomen was not distended, but there was marked tenderness in both lower quadrants, especially on the right side. There were also some rigidity and rebound tenderness in the right lower quadrant. On vaginal examination, the cervix was softened but closed and the size of the uterus could not be determined because of the tenderness of the abdomen. A small, tender, cystic mass was felt in the right fornix. In the posterior cul-de-sac, to the left of the midline and just beneath the vaginal mucosa, a nail could be easily palpated. The rectovaginal septum was tender and indurated. Speculum examination of the vagina and cervix did not show any signs of recent trauma. A flat plate of the abdomen showed the nail lying on the left side of the pelvis (Fig. 1).

The following morning, under general anesthesia, the vaginal mucosa overlying the nail was transversely incised. The head of the nail was exposed by sharp and blunt dissection and the entire nail, 4 cm. long and quite rusty was then extracted from the surrounding tissue in which it was very firmly imbedded. It was noted that the peritoneum had been opened during this procedure, although it could not be ascertained whether the nail itself had penetrated the peritoneum. A rubber drain was placed in the opening and a small amount of gauze packing was placed against the cul-de-sac.

The patient was given antibiotics and tetanus and gas gangrene antitoxin postoperatively. Her course was uneventful except for a low-grade fever for 7 days. The drain was

gradually shortened and completely removed on the fourth postoperative day. An Aschheim-Zondek test done prior to the patient's discharge was negative. Pelvic examination on the day of discharge showed some nontender residual induration in the rectovaginal septum.

Throughout her hospital stay, the patient steadfastly denied knowing how the nail had entered the pelvis. She suggested that she "might have swallowed it" or else that it had entered the vagina when she fell off a ladder several weeks earlier.

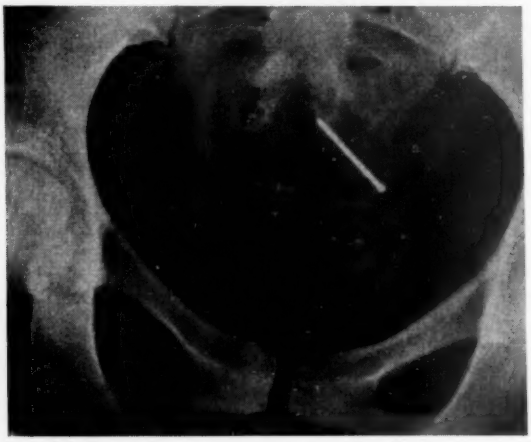

Fig. 1.—X-ray of the abdomen in the recumbent position, showing a nail on the left side of the pelvis.

Comment

It seemed best here to remove the nail without further expectant treatment. It was easily accessible and the patient had developed parametritis and signs of peritoneal irritation. There appeared to be little to gain by further delay.

We wish to thank Mr. E. Entin for the photograph.

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FETAL WASTAGE AT THE SLOANE HOSPITAL FOR WOMEN

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A CERTAIN number of pregnancies result in the loss of the fetus by abortion, stillbirth, or death within the neonatal period. The sum total of all pregnancies so lost constitutes the fetal wastage. It is of value to record this wastage, first in order that we may be aware of what is occurring, and, second, so that our attention may be drawn to the causes of such wastage. For these reasons, a study has been made of all pregnancies which terminated in fetal loss on the obstetrical service of the Sloane Hospital for Women during the years 1934-1955, inclusive.

Material and Method

In all of the cases studied, delivery was on the ward service of the Sloane Hospital for Women. During this time there were a total of 44,124 pregnancies terminated, of which 4,003 resulted in fetal wastage. These cases were divided into the following groups: under 20 weeks (abortions); 20-27 weeks (previable prematures); 28-37 weeks (prematures); and 38 or more weeks (term births). The total number of cases in each group was determined for each year. The causes for the fetal loss were taken from the chart, a division of each group was made according to cause, and rates were determined.

The rates were defined in two ways, according to the total number of pregnancies terminated, and according to the number of births at 20 or more weeks. The first definition, according to the total number of pregnancies terminated, becomes useful in determining the probability of fetal wastage at various stages of pregnancy, and to some extent allows a comparison to be made of the effects of abortion and premature delivery. The second definition, according to the number of births at 20 or more weeks, is similar to the one usually used in defining fetal mortality, except that the "previable prematures" are included. This is an important point of differentiation.

Abortions are all pregnancies which terminated before the twentieth week, and are divided into spontaneous and therapeutic. All these patients had registered in the Ante-Partum Clinic until 1950. Unregistered patients with abortions during the period of this study were cared for on the gynecological service until 1950, and are not included in the study; after 1950 they do appear in the study. The abortion figures, therefore, give the abortion rate *for patients already registered* until 1950, but not after this. These patients usually register during the third month of gestation. The number who have abortions before they can register is unknown. The rate is, therefore, not the true expectancy of abortion in women who have successfully passed at least the first 2 months.

Fetal loss occurring at or after the twentieth week is considered in three groups: 20-27 weeks; 28-37 weeks; and 38 or more weeks. Stillbirths and neonatal deaths are grouped together in each of the groups. This grouping is necessary because the problems are different in each group, and because the neonatal deaths in the 20-27 week group exert a strong influence on the over-all fetal mortality.

Results

1. Fetal Wastage.—The total fetal wastage is presented by years in Fig. 1. During this time 44,124 pregnancies terminated on the ward service: 2,549 by abortion (spontaneous or therapeutic) and 41,575 by delivery on or after the twentieth week. In the latter group, there were 1,454 stillbirths and neonatal deaths. Based on the total number of terminated pregnancies, the fetal wastage is 90.4 per thousand, made up of spontaneous abortion 43.2 per thousand; therapeutic abortion 14.2 per thousand; and fetal mortality on or after the twentieth week 33.0 per thousand. These rates indicate that in the years 1934-1950 2.9 per cent of the patients registered for antepartum care have aborted spontaneously. From 1934-1955, 1.4 per cent have had therapeutic abortions, and 3.3 per cent have lost the baby on or after the twentieth week. These groups are considered separately.

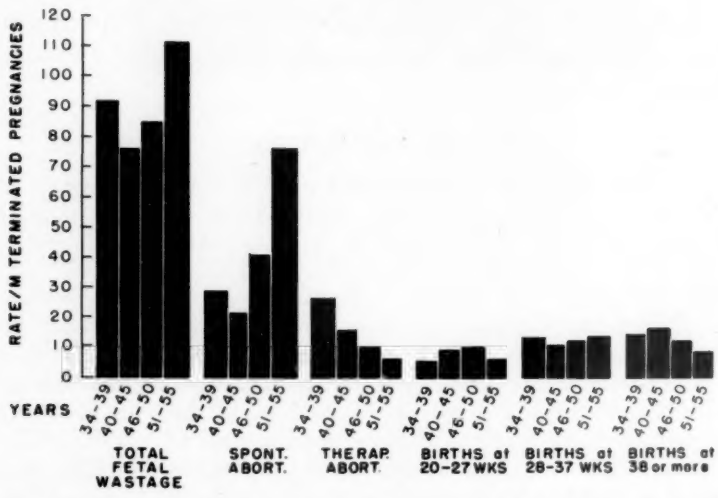

Fig. 1.—Fetal wastage at various stages of pregnancy for the years 1934-1955; rate per thousand terminated pregnancies.

2. Spontaneous Abortion.—The over-all rate for spontaneous abortion for the years 1934-1950 is 2.9 per cent. This appears to be very low, in view of the usually accepted abortion rate of about 10 per cent. In the years 1951-1955 the rate is 7.9 per cent. The rates shown in Table I (taken from their respective annual reports) for the following hospitals may be compared with this.

It is obvious that there is a wide variation in the reported rates for abortion. This is apparently due in part to admission policy, patients with abortions being admitted to the gynecological service rather than the obstetrical service in many hospitals. The time at which the patient registers for obstetrical care is also important, for a certain number abort before they can register. Some of these patients do not require hospitalization, and cannot be counted. Others are admitted to the gynecological service at the Sloane Hospital for

Women and also are not counted in the obstetrical figures. The great majority (85 per cent) of the patients in this study registered after the second missed period, and the abortion rate of 2.9 per cent is therefore that of a special group. The yearly rates for spontaneous abortion are shown in Fig. 1.

TABLE I. SPONTANEOUS ABORTION RATES FROM VARIOUS HOSPITALS

HOSPITAL	YEARS	RATE %
Chicago Lying-in	1931-1941	3.0
	1941-1946	5.3
	1946-1950	3.8
	1950-1951	7.8
Johns Hopkins	1949	7.4
University of Maryland	1950-1951	2.2
New York Lying-In	1949	8.1
University of California	1950-1951	6.7
Sloane Hospital for Women	1934-1950	2.9

The wide variation, especially the decrease during the war years, cannot be explained. It is possible that admission policy may have excluded some patients at a time when the hospital staff was depleted, but the number thus excluded would have to be small, first, because the policy of taking complete care of registered patients remained in force, and, second, because the question of admission has always been decided on medical grounds. Nevertheless, such factors must be considered during the period 1944-1950. In the years 1951-1955, the great increase in the number of abortions is clearly due to admission policy. During this time, the unregistered patients formerly admitted to the gynecological service were admitted to the obstetrical service.

It is obvious that the reported incidence of spontaneous (or nontherapeutic) abortion is meaningless, except as a record of the number of cases seen. It would be unwise to try to extract from these figures the likelihood of spontaneous abortion in general.

3. Therapeutic Abortion.—The yearly rates for therapeutic abortion are shown in Fig. 1. There is a downward trend, which reached the rate of 1.5 per thousand for 1955. This trend has been steady during the years under study. This continued decrease in the number of therapeutic abortions is related to a decreasing number of medical complications in general, and to improved methods of managing those complications. There is no correlation whatever between the rates for spontaneous and for therapeutic abortion.

4. Perinatal Mortality.—This is generally expressed as the combined stillbirth and neonatal death rate, based on the number of births occurring on or after the twenty-eighth week. When this calculation is made, the over-all fetal mortality is 27.8 per thousand, with 1,118 stillbirths and neonatal deaths in 41,203 deliveries on or after the twenty-eighth week. But there were an additional 245 infants who were born alive between the twentieth and twenty-seventh week and who subsequently died. When these are added to those lost on and after 28 weeks, the fetal mortality becomes 33.2 per thousand. The group born between 20 and 27 weeks therefore is an important one, and it must be considered when the causes of perinatal mortality are calculated.

There are several ways in which the perinatal mortality rate can be calulated. It is possible to use, as a base figure, all terminated pregnancies. This would yield a figure of 30.9 per thousand, but the base is false because the number of pregnancies terminated before 20 weeks is due, in this series, to admission policy and not to the natural course of pregnancy.

In calculating the perinatal mortality rate, it is therefore necessary to use the total number of births occurring on or after the twentieth week. The over-all rate, for the 22 years studied, is 37.4 per thousand. The variation in this rate is shown in Fig. 2. A gradual trend downward is apparent, but this is not very striking.

The total perinatal mortality rate is a composite rate, made up of results in three quite different groups of infants: those born at 20-27 weeks; those born at 28-37 weeks; and those born at term. It is necessary, therefore, to study each group separately. To begin with, the number of fetal losses in each group for each year can be related to the total number of births on or after the twentieth week. This relation is shown in Fig. 2. The over-all perinatal mortality shows a slight downward trend. The rate for the group born at 38 or more weeks shows a distinct downward trend. The rate for the group born at 28-37 weeks shows no trend. The rate for the group born at 20-27 weeks shows a rising trend.

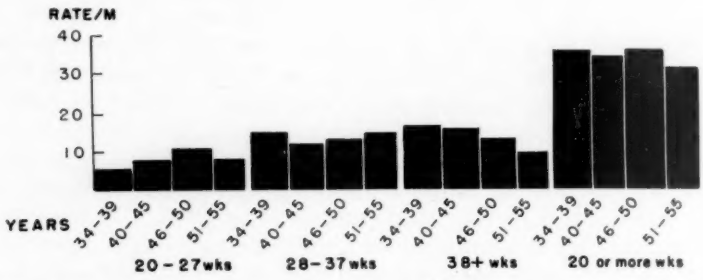

Fig. 2.—Perinatal mortality in each group of cases for the years 1934-1955; rate per thousand births at 20 or more weeks.

This method of calculation, however, obscures the events in the two premature groups, since the largest portion of the base figure is the number of infants born at term. It is worth while, then, to relate the fetal loss *in each group* to the number of infants born *in each group*. This calculation is shown graphically in Fig. 3. These figures show a downward trend in the groups born at term, and at 28-37 weeks, but the group born at 20-27 weeks shows a steady and very high mortality rate.

It appears from these graphs that real improvement has been made in reducing fetal mortality in two of the groups, but that the sum of the parts shows less improvement. The cause for this lies in an increasing *number* of births in both of the premature groups, as shown in Fig. 4. There has been an increase in the total number of births but the increase in the premature groups represents both an absolute and relative increase. The over-all perinatal mortality in the group born at 20-27 weeks is 90.5 per cent (336 deaths in 371 cases) and in the group born at 28-37 weeks is 16.5 per cent (548 deaths in 3,326 cases) so that relative increases in these groups rapidly increase the over-all perinatal mortality. The increase in numbers in these groups has nearly balanced out the improvement in care of all three groups. The cause for this increase in premature births is not apparent, but the same increase is seen in the figures for New York City as a whole in the years 1940-1951.[1]

5. Causes of Fetal Mortality—All Groups.—These are based principally on the results of autopsy examination (the autopsy rate being 96.7 per cent), and are listed in numerical order in Table II. The yearly variations are shown in Fig. 5.

Prematurity: Prematurity is the largest single cause of death, accounting for 465 deaths (32 per cent of all deaths). This represents a rate of 11.3 per

thousand. This cause of death does not necessarily indicate the *obstetrical* cause of the premature birth and subsequent death, but emphasizes that failure to keep these infants alive is the greatest single reason for perinatal mortality found in this study. The graph of yearly variations shows no downward trend, and once again it is necessary to study each group separately. When this is done it is seen that there has been a downward trend in the group born from 28-37 weeks. The management of cases of prematurity has therefore produced definite improvement, but the increasing numbers of premature infants have caused the *over-all* rate to remain essentially unchanged.

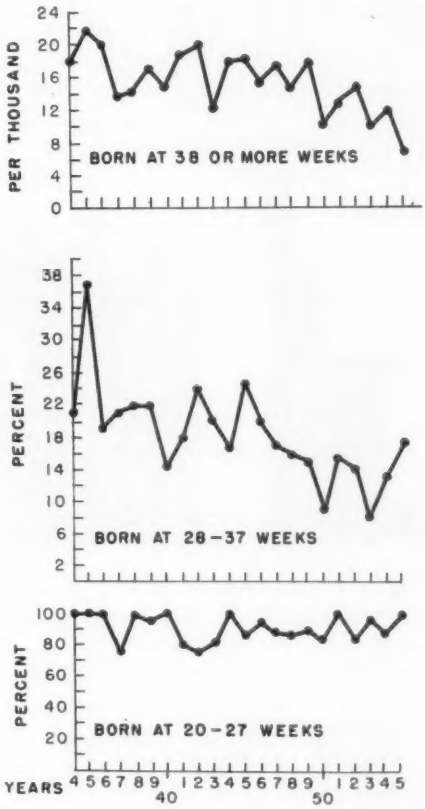

Fig. 3.—Perinatal mortality in each group of cases. Rate based upon the number of infants born in each group, per *thousand* in the group born at 38 or more weeks; per *cent* in the premature groups.

Maceration: This pathological classification represents a varied group of obstetrical causes. The most important of these is maternal disease, particularly toxemia. This cause remains essentially unchanged, and accounts for a fetal mortality rate of 7.5 per thousand over the period studied.

Asphyxia: This pathological classification represents a variety of obstetrical causes, from cord accidents to placenta previa and premature separation of the placenta. There is a downward trend in the latter half of the period studied. This cause of death accounts for a rate of 4.0 per thousand.

Congenital defect: These are infants with anatomical defects incompatible with life. There was a slight rising trend in the first years of the study, and a falling trend since then. This cause represents a rate of 4.1 per thousand.

TABLE II. THE CAUSES OF PERINATAL DEATHS BASED UPON BIRTHS AT 20 OR MORE WEEKS, ACCORDING TO ORDER OF FREQUENCY

CAUSES	NO. OF CASES	RATE PER THOUSAND BIRTHS AT 20 OR MORE WEEKS
1. Prematurity	465	11.3
2. Maceration	310	7.5
3. Congenital defect	167	4.1
4. Asphyxia	163	4.0
5. Unknown	137	3.3
6. Birth trauma	84	2.0
7. Other	45	1.1
8. Hemolytic disease	42	1.0
9. Placental insufficiency	23	0.5
10. Pneumonia	17	0.4
11. Syphilis	3	0.07
Total	1,456	35.27

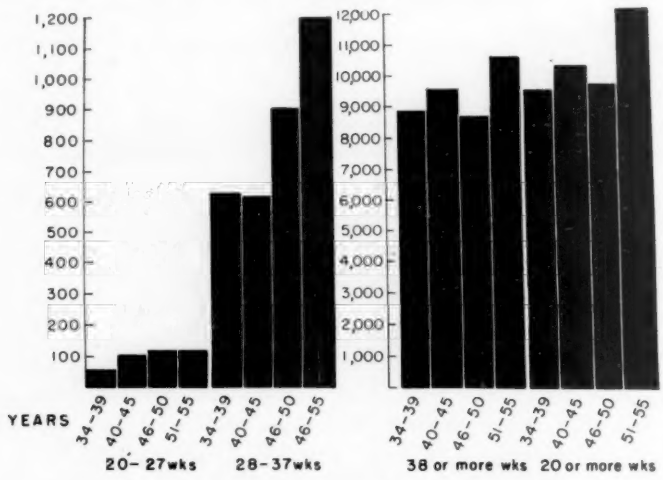

Fig. 4.—Total number of births in each group during the years 1934-1955.

Unknown: These are cases in which the cause of death cannot be determined pathologically or clinically. The over-all rate is 3.3 per thousand, and there is a slight downward trend in the period studied.

Birth trauma: These are clear-cut cases in which death is due to demonstrable injury incurred during birth. The over-all rate is 2.0 per thousand. There is a real downward trend in this category, so that for the last 5 years of the study the rate was 0.5 per thousand.

Other causes: These causes account for 3.0 deaths per thousand births, and the number of cases in each group is too small to justify statistical examination or search for trends.

6. The Causes of Fetal Mortality at 20-27 Weeks.—There were 371 babies born in this group, 336 of whom died. The fetal mortality is therefore 90.5 per cent. It is remarkable that 9.5 per cent of these "previable prematures" survived the neonatal period.

The fetal mortality in this group is due principally to prematurity, which accounts for a rate of 71.0 per cent. Next comes maceration with death due to some maternal factor, accounting for a rate of 9.8 per cent. The remainder of the causes of death are so few as to be insignificant.

7. The Causes of Fetal Mortality at 28-37 Weeks.—There were 3,326 babies born in this group, 548 of whom died. The fetal mortality rate is therefore 16.5 per cent. Though these babies are premature, 83.5 per cent survive the neonatal period.

The principal cause of fetal mortality in this group is, again, prematurity, which produces a rate of 6.3 per cent. This is followed closely by maceration, with a rate of 4.1 per cent. Congenital defect accounts for 2.0 per cent, asphyxia for 1.0 per cent, and unknown for 1.3 per cent. The remainder are insignificant.

8. The Causes of Fetal Mortality at Term.—There were 37,877 babies born at 38 or more weeks, of whom 569 died. The fetal mortality is therefore 15.0 *per thousand.* Conversely, 98.5 per cent of these children born at term survive the neonatal period.

The chief cause of death at term is maceration, which accounts for a rate of 3.2 per thousand. This is closely followed by asphyxia, 3.0 per thousand, congenital defect, 2.2 per thousand, unknown, 2.1 per thousand, and birth trauma, 1.6 per thousand.

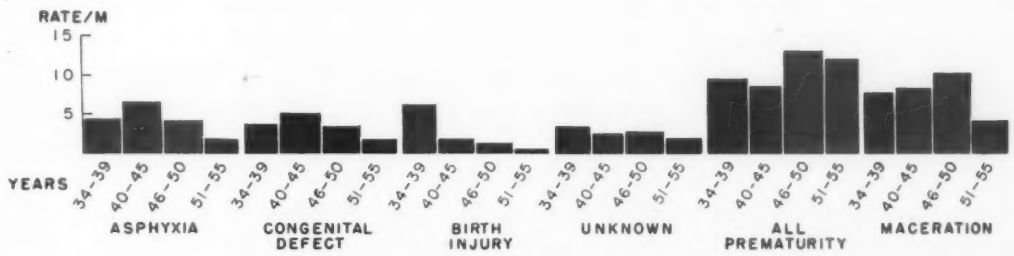

Fig. 5.—Fetal mortality from various causes grouped by years; rate per thousand births at 20 or more weeks.

9. Order of Causes of Fetal Mortality by Groups (Table III).—The ten leading groups which go to make up the final numerical rate of perinatal mortality are shown in Table III. Prematurity accounts for the first two and represents a rate of 11.3 per thousand. Most striking is the fact that the leading single cause of perinatal death is prematurity in the period from 20 to 27 weeks. Thus the group with the smallest number of births accounts for the largest number of deaths both absolutely and relatively. Conversely, the term group, which accounts for 92 per cent of all births, is not represented in this list until the fourth place.

TABLE III. CAUSES OF PERINATAL DEATHS IN ORDER OF RATE BY GROUPS

CAUSES	CASES	RATE PER THOUSAND BIRTHS AT 20 OR MORE WEEKS
1. Prematurity at 20 to 27 weeks	259	6.3
2. Prematurity at 28 to 37 weeks	204	5.0
3. Maceration at 28 to 37 weeks	136	3.3
4. Maceration at 38 or more weeks	134	3.2
5. Asphyxia at 38 or more weeks	124	3.0
6. Congenital defect at 38 or more weeks	92	2.2
7. Unknown at 38 or more weeks	86	2.1
8. Congenital defect at 28 to 37 weeks	67	1.6
9. Birth trauma at 38 or more weeks	66	1.6
10. Maceration at 20 to 27 weeks	31	0.8

Comment

Fetal wastage at the Sloane Hospital for Women has been considered in three groups: spontaneous abortions, therapeutic abortions, and perinatal mortality at or after the twentieth week of gestation. It appears that, once a patient has registered (usually in the third month), the likelihood of a spontaneous abortion is 2.9 per cent. This figure has varied for undetermined reasons, and now appears to be rising. Over the period studied, a further 1.4 per cent have required therapeutic abortion, but this figure has declined steadily and was 0.15 per cent in 1955.

Having passed the period of possible abortion, the patient has a less than 1 per cent (0.89 per cent) probability of being delivered during the twentieth to twenty-seventh weeks. If delivery does occur during this time, the perinatal mortality is 90.5 per cent. The probability of delivery during the period from the twenty-eighth to the thirty-seventh week is 8.0 per cent, and if delivery does occur during this time the perinatal mortality is 16.5 per cent. Thus, 91.1 per cent of those who do not abort will be delivered at term, with a perinatal mortality of 1.5 per cent.

The perinatal mortality rate has shown a slight downward trend over the 22 year period studied. This trend would be more marked except for a relative as well as an absolute increase in the number of premature infants born each year. When the groups (at 20-27 weeks; 28-37 weeks; and 38 or more weeks) are studied separately, it is seen that there has been a decrease in the perinatal mortality rate in the groups born at term and at 28-37 weeks, *when the calculation is based on the number of births in each group,* but this improvement is canceled out by the increasing numbers of premature infants.

This factor is emphasized by calculation of the perinatal mortality rate for the years 1934-1939, using the number of deliveries in 1951-1955. The great difference lies in the fact that there were 1,194 infants born from 28-37 weeks in 1951-1955, and 621 in 1934-1939. The perinatal mortality rate for this group fell from 22 per cent to 14.4 per cent during this time, but the net result was an absolute increase in the number of deaths from 137 in 1934-1939 to 172 in 1951-1955. When these are added to the figures for the years 1934-1939, the perinatal mortality rate is 46 per thousand. The true change in results is therefore represented by a drop from 46 to 31.9, a decrease of 14.1 per thousand. This demonstrates an improvement in the perinatal mortality rate of nearly one third.

The leading cause of perinatal mortality on and after the twentieth week is prematurity, even though this by definition cannot be applied to the group born at term. This cause shows relative improvement. There is a real decrease also in the perinatal mortality due to birth trauma. These two causes account for a combined rate of 13.3 per thousand over the 22 year period, or approximately one third of the total number of fetal deaths. The remaining causes (of two thirds of the fetal deaths) have shown no significant change. These causes are related to disease in the mother, to the accidents of pregnancy and labor, and to unknown factors. If further improvement is to be made in

these latter categories, there must be improvement in maternal health through social and hygienic measures, and greater knowledge of the causes of congenital defects and of such accidents as placenta previa must be obtained.

On the other hand, the one cause of fetal death most susceptible to treatment, birth trauma, has been almost eliminated. The management of premature labor, and of the premature infant, has improved. This leaves, as the one field in which great improvement can theoretically be made, the prevention of premature delivery.

Reference

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CARDIAC SURGERY ASSOCIATED WITH PREGNANCY

A Report of 27 Cases*

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THE decline of infection, toxemia of pregnancy, and hemorrhage as leading causes of maternal death has been accomplished by the introduction of antibiotic drugs, the use of antihypertensive agents, and the widespread and safer utilization of whole blood transfusions, respectively. As a result, heart disease has become the primary cause of death of the parturient woman.

Jensen,[1] Bunim and Appel,[2] Gordon,[3] and Mendelson[4] have all reported on maternal mortality due to heart disease and have emphasized the need for immediate recognition of the condition and its energetic treatment in order to decrease the number of needless maternal deaths. Despite the initiation of all generally recognized methods of therapy such as rest, diuretics, sodium-free diet, and digitalization, there are still far too many pregnant patients sacrificed needlessly each year. It is now felt that certain of these patients can be salvaged and given a new life which will be free from the ever-present threat of heart failure, if their specific cardiac lesion is amenable to surgical correction.

A report of the experience of the United States Naval Hospital, San Diego, California, in the field of cardiac surgery associated with and during pregnancy affords the basis for this paper and may be considered as a preliminary report.

History of Cardiac Surgery

Klebs[5] in 1876, MacCallum and McClure[6] in 1906, and Cushing and Branch[7] in 1908 first reported experimental work on valvular surgery in dogs. In 1924 Cutler, Levine, and Beck[8] reported 5 cases of mitral valvulotomy in human beings with one survival.

Since 1947, Smithy,[9] Bailey,[10] and Harken[11] have successfully rekindled interest in the surgery of the heart and great vessels. It is due entirely to

*This work is not to be construed as necessarily reflecting the views of the Department of the Navy.

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the vision and untiring efforts of such pioneers that cardiac lesions can now be successfully corrected by surgery with a minimum of morbidity and mortality.

With surgery of the heart in nonpregnant women and males accepted in the majority of surgical circles, it was not long before this particular medium of therapy was considered seriously in the correction of certain selected valvular and congenital lesions in pregnant women. Cooley and Chapman[12] reported mitral commissurotomies performed on 2 primigravid patients at 23 and 28 weeks' gestation, respectively, and both were delivered vaginally of viable infants. Logan and Turner[13] reported mitral commissurotomies on 2 pregnant women. One developed a hemiplegia when operated upon at 16 weeks' gestation but was delivered of a viable infant vaginally at 32 weeks' gestation. Brock[14] reported successful results in commissurotomies performed upon 3 gravid women at 12, 28, and 28 weeks, respectively, all of whom had a vaginal delivery of a viable infant. Parkinson[15] reported a valvulotomy on one primigravida with tuberculosis at 9 weeks' gestation; the infant was undelivered at the time of his report. Baker, Brock, Campbell, and Wood[16] reported 3 operations at 12, 28, and 28 weeks, respectively, and all 3 patients were delivered of viable infants vaginally. Burwell and Ramsey[17] reported 7 cases; 5 were successful and complications developed in 2. One patient died as a result of irreversible pulmonary vascular changes and the other patient had to have a therapeutic abortion because of serious mitral insufficiency which developed postoperatively. Mason[18] reported 4 cases with one death but no details were available. Rumel,[19] Sommerville,[20] Tillman,[21] Gorenberg,[22] and Watt, Bigelow, and Greenwood[23] accounted for 13 successful operations without a maternal death. Mendelson[4] reported 5 operations at 19, 18, 17, 17, and 19 weeks' gestation. Two patients were delivered vaginally of viable infants at term without difficulty. One was delivered of a viable infant at 35 weeks and developed transient puerperal fibrillation and pulmonary embolism but recovered. The remaining 2 patients developed transient fibrillation; one had an uncomplicated delivery at term and the other was delivered vaginally at 28 weeks, but the infant died as a result of prematurity. Burwell and Ramsey[17] mentioned 15 patients with pregnancies subsequent to mitral valvulotomy, all of whom were delivered without cardiac difficulty. Mendelson[4] reported 2 similar cases; one of these patients had an abortion at 16 weeks because of large fibromyomas of the uterus. At the United States Naval Hospital, San Diego, California, there have been 27 cases of cardiac surgery associated with pregnancy, 8 of which were performed during pregnancy. The results obtained in each case are contained in the report to follow.

TABLE I. TYPE AND DISTRIBUTION OF SPECIFIC LESIONS CORRECTED BY SURGERY

TYPE OF LESION	NO.	%
Rheumatic mitral stenosis	25	64.0
Patent ductus arteriosus	5	12.8
Coarctation of aorta	4	10.3
Congenital pulmonic stenosis	1	2.6
Congenital aortic stenosis	1	2.6
Intra-auricular defects	2	5.1
Congenital fibrinous constriction of superior vena cava	1	2.6
Total	39	100.0

Material for Study

During the 4 year period from 1953 to 1956, inclusive, there have been 39 operations on the heart or great vessels of female patients over 15 years

TABLE II. PATIENTS OPERATED UPON WHILE NOT PREGNANT

INITIALS	CASE	AGE	GRAVIDITY	PARITY	ABORTION	DIAGNOSIS	THERAPEUTIC ABORTIONS	STERILIZATION	DATE OF OPERATION	OPERATION	RESULTS
K. B.	No. 1	39	i	i	0	Mitral stenosis	0	0	8/18/55	Commissurotomy	Improved. Had cerebrovascular embolism prior to operation
H. B.	No. 2	44	i	i	0	Mitral stenosis with right renal infarct	0	0	7/ 8/54 8/10/54	Right nephrectomy Commissurotomy	Improved. Embolus right mid-cerebral artery. Subacute bacterial endocarditis 6/56
V. H.	No. 3	21	i	i	0	Congenital pulmonic stenosis	0	0	5/26/55	Broch repair	Marked improvement
R. L.	No. 4	37	xii	iii	ix	Mitral stenosis	Many induced	+	2/54	Commissurotomy	Improved. Previous drug addiction
C. H.	No. 5	36	iv	iii	i	Mitral stenosis	0	+	2/24/54	Commissurotomy	Complete relief
B. B.	No. 6	22	ii	ii	0	Patent ductus arteriosus	0	0	7/22/54	Difficult closure	Postoperative convulsions. Died 7/23/54
R. C.	No. 7	18	ii	i	i	Congenital aortic stenosis	0	+	5/13/54	Transventricular aortic valvulotomy	Marked improvement
K. A.	No. 8	42	i	i	0	Mitral stenosis	0	0	8/ 3/55	Commissurotomy	Improved. Some episodes decompensation
G. W.	No. 9	33	iii	iii	0	Mitral stenosis	0	+	7/28/55	Commissurotomy	Improved. Did not want operation during pregnancy

E. C.	No. 10	–	ii	ii	0	Coarctation at operation	0	0	1/19/55	Exploratory thoracotomy	No improvement
C. G.	No. 11	–	ii	ii	0	Patent ductus arteriosus	0	0	6/ 5/56	Closure	Excellent result
V. K.	No. 12	34	i	i	0	Patent ductus arteriosus	0	0	6/ 6/56	Closure	Excellent result
J. C.	No. 13	22	i	i	0	Mitral stenosis	0	0	11/30/53	Commissurotomy	Marked improvement
M. R.	No. 14	30	vi	iv	ii	Severe mitral stenosis	0	+	2/ 2/55	Commissurotomy	Died third postoperative day. Aschoff bodies at post mortem. Decompensation with all pregnancies
A. M.	No. 15	19	i	i	0	Mitral stenosis	0	+	6/ 2/55	Commissurotomy 50 per cent regurgitation	Stenosis helped, pregnancy still intact
J. H.	No. 16	19	i	i	0	Patent ductus arteriosus	–	–	11/ 4/53	Closure	Excellent result
F. T.	No. 17	–	ii	ii	0	Patent ductus arteriosus	0	0	11/19/53	Closure	Good result. One pregnancy after closure
M. A.	No. 18	41	ii	i	i	Mitral stenosis	i	+	7/27/53	Commissurotomy	Poor result. Pregnancy after operation produced decompensation and therapeutic abortion and ligation done
M. D.	No. 19	48	i	i	0	Mitral stenosis	0	0	10/24/56	Commissurotomy	Improved. Postoperative wound infection. Had cerebrovascular embolus prior to operation

TABLE III. PATIENTS OPERATED UPON DURING PREGNANCY

INITIALS	CASE	AGE	GRAVIDITY	PARITY	WEEKS' GESTATION	DIAGNOSIS	DECOMPENSATION	OPERATION	FINDINGS AT OPERATION	MATERNAL AND FETAL RESULTS
E. S.	No. 1	20	ii	i	11	Coarctation of aorta	–	Resection of coarctation	Coarctation	Good result. Delivered of term viable infant spontaneously without anesthesia
G. S.	No. 2	18	i	0	18	Coarctation of aorta	–	Resection of coarctation	Coarctation	Good result. Viable infant delivered by forceps rotation at term
H. M.	No. 3	33	iv	iii	14	Mitral stenosis	+	Commissurotomy attempt	Stenosis and insufficiency	Died at operation
C. W.	No. 4	20	iii	ii	15	Mitral stenosis	+	Commissurotomy	Stenosis	Good result. Spontaneous delivery of viable infant at term under pudendal block
B. H.	No. 5	25	i	0	17	Mitral stenosis	++	Commissurotomy	Stenosis	Good result. Low forceps delivery of term infant under pudendal block
V. S.	No. 6	27	i	0	22	Mitral stenosis	+	Commissurotomy	Stenosis	Good results. Infant delivered at 31 weeks. Died on fifth day of congenital heart disease
B. R.	No. 7	25	ii	i	24	Mitral stenosis	+	Commissurotomy	Stenosis	Good result. Delivered of term infant by outlet forceps under pudendal block
M. J.	No. 8	35	iv	iii	29	Mitral stenosis	+	Commissurotomy	Stenosis	Good result. Delivered of Mongoloid infant by breech at term without anesthesia

of age at this hospital. The type and distribution of specific lesions are listed in Table I. This figure does not include patients who underwent cardiac catheterization or those who required massage subsequent to cardiac arrest which complicated some other primary surgical procedure. Twelve of these patients were nulligravidas and will not be considered further in this report. Eight of the remaining 27 patients were operated upon during a pregnancy. The data concerning the 19 patients not operated upon during a pregnancy are summarized in Table II.

Patients Not Operated Upon During Pregnancy.—This group of 19 patients had a total of 46 pregnancies. Thirty-two of these terminated in full-term deliveries. One infant was Mongoloid and died. There were 13 abortions prior to operation, 9 of these in one patient and all admittedly induced, but not because of her cardiac status. One patient had a commissurotomy following a pregnancy complicated by cardiac decompensation. In a subsequent pregnancy, therapeutic abortion and sterilization were performed because severe decompensation developed in the third month of gestation. There were 3 operative deaths in the 27 patients or an 11 per cent mortality. Nineteen, or 70 per cent, showed marked improvement following operation and only 2, or less than 8 per cent, failed to show any improvement. Of the remaining 3 patients, 2 developed embolic phenomena that produced some paralysis and paresis prior to operation and one had an embolus of the right middle cerebral artery following operation. All 3 patients have since shown marked improvement.

Patients Operated Upon During Pregnancy.—The data on the 8 patients operated upon during pregnancy are contained in Table III. Their case histories are recorded here in more detail:

CASE 1.—E. S., aged 20, was first admitted on Oct. 21, 1954, because of hypertension. Her last menstrual period was on Feb. 26, 1954, and the estimated date of confinement Dec. 3, 1954. She had been followed in a prenatal clinic elsewhere and frequent high blood pressure readings were noted. She was considered to have essential hypertension until the spontaneous delivery of a 5 pound, 13½ ounce male infant on Nov. 7, 1954. The postpartum blood pressure remained elevated and she was discharged on the seventh postpartum day with a blood pressure of 154/104. In April, 1955, she had a pre-employment physical examination and the physician noted coldness of the lower extremities. Further studies revealed and confirmed a coarctation of the aorta. On May 11, 1955, this was surgically corrected and her postoperative course was uneventful. Although she was 11 weeks pregnant at this time, the diagnosis of pregnancy was not made. On July 21, 1955, she reported to the prenatal clinic and was found to be in the twentieth week of gestation. The last menstrual period had been Feb. 28, 1955. She had no subsequent prenatal examinations and entered the hospital in active labor on Nov. 29, 1955, and was delivered of a 7 pound, 9 ounce viable male infant spontaneously under pudendal block anesthesia shortly after admission. Her postpartum course was uneventful. She has since undergone an uncomplicated third pregnancy with delivery of a normal full-term infant.

CASE 2.—G. S., aged 18, had a diagnosis of active rheumatic fever at the age of 10 and was treated with bed rest for 6 months. Her activities were restricted until she entered high school at which time she was allowed to take regular physical education. She had no recurrence of symptoms of cardiac distress. She was first seen in the prenatal clinic on Nov. 18, 1955. Her last menstrual period was on July 7, 1955, and the estimated date of confinement was April 14, 1956. Coarctation of the aorta was suspected and the diagnosis confirmed by chest x-ray and blood pressure studies. No clinical evidence of rheumatic fever was detected. On Dec. 13, 1955, during the eighteenth week of pregnancy, the coarctation was surgically removed. She was followed in the Abnormality

Prenatal Clinic and entered the hospital on April 26, 1956, for induction of labor. Induction was attempted with 1 c.c. Pitocin in 1,000 c.c. of 5 per cent glucose intravenously on April 27, 1956, and was unsuccessful. She was allowed to rest overnight and started into spontaneous labor on April 28, 1956, and was delivered of an 8 pound, 6 ounce viable infant after Kielland forceps rotation under pudendal block anesthesia.

CASE 3.—H. M., a 33-year-old Caucasian woman, was admitted to this hospital on Feb. 11, 1955, because of known rheumatic heart disease following rheumatic fever at the age of 16. A heart murmur had been detected at the age of 18. During her first pregnancy at 26 she had an attack of hemoptysis at 6 months' gestation; otherwise the prenatal course was normal. She had two subsequent pregnancies when she was 29 and 31. With each of these she experienced severe decompensation during and following the sixth month of gestation. She was first seen in the third month of her fourth pregnancy. Examination confirmed a diagnosis of rheumatic mitral stenosis without evidence of concomitant regurgitation. She had no clinical evidence of congestive failure, although she noted definite dyspnea with moderate exertion. By virture of her unfavorable past history the consultant in cardiology recommended digitalization to be followed by mitral valvulotomy. On Feb. 16, 1955, in the fourteenth week of gestation, cardiotomy was performed. The mitral valve was markedly stenotic and fibrotic, with shortened and fused chordae tendinae. Splitting of the commissure was ineffectual and the guillotine finger knife was inserted, cutting the commissure. At this point abnormalities were noted in the electrocardiogram and the surgeon reported the appearance of marked regurgitation through the mitral orifice. Three sutures were placed through the annulus and the valve in an effort to correct the incompetence. In spite of this the electrocardiogram revealed progressive deterioration and the operation was abandoned. The heart was closed and the chest was closed rapidly. At the termination of the procedure the peripheral pulses and blood pressure were not obtainable and the electrocardiogram showed grossly abnormal complexes. The chest was reopened and the heart massaged for one hour without effect. The patient was pronounced dead at 11:31 A.M. on Feb. 15, 1955.

CASE 4.—G. W., aged 20, had a history of active rheumatic fever at the age of 11. She was treated with complete bed rest for 2 months. Her history showed that she was blood type O, Rh negative, and that her husband was type A, Rh positive. During her first pregnancy she had moderate dyspnea. She was delivered of a 6 pound, 14 ounce female infant spontaneously on July 5, 1954, without complication. During her second pregnancy symptoms of cardiac distress were increased and she was hospitalized throughout the last month of pregnancy. She was delivered of a 5 pound, 11 ounce female on July 6, 1955, without further difficulty. She had severe nausea and vomiting during the first trimester of her third pregnancy. The last menstrual period was on Oct. 29, 1955, and the estimated date of confinement Aug. 3, 1956. During the second month of gestation she became dyspneic and hemoptysis occurred. She was then digitalized. Clinical findings at this time were highly compatible with a tight rheumatic mitral stenosis. She was admitted to the hospital on Feb. 1, 1956, on the recommendation of the cardiac consultant. A commissurotomy was done on Feb. 15, 1956, in the fifteenth week of gestation. She was discharged on the tenth postoperative day, markedly improved. On July 19, 1956, she was readmitted to the hospital in early labor and was spontaneously delivered of a 7 pound, 6½ ounce male infant under pudendal block anesthesia.

CASE 5.—B. H., aged 25, had a history of St. Vitus' dance at the age of 13, treated with partial bed rest. During the next 2 years approximately one-half of her time was spent in bed. The last menstrual period was on Feb. 25, 1954, and the estimated date of confinement Dec. 1, 1954. Exertional dyspnea occurred in the eighth week of pregnancy and increased until her admission to the hospital on June 5, 1954. A diagnosis of mitral stenosis was established and a mitral commissurotomy was performed on June 24, 1954, in the seventeenth week of gestation. The mitral orifice was enlarged from 6 to 25 mm. She was discharged on July 9, 1954, after an uneventful recovery. She was readmitted on Nov. 18, 1954,

because of one episode of hemoptysis. She went into spontaneous labor on Dec. 17, 1954, and was delivered of a 6 pound, 8 ounce male infant by low forceps under pudendal block anesthesia without difficulty. Her postpartum course was completely uneventful and she was discharged on the tenth postpartum day.

CASE 6.—V. S., aged 27, had a history of severe tonsillitis at the age of 13 with a subsequent prolonged fever and swelling of the joints of the feet. She was told she had a "heart murmur" at the age of 19. This was apparently not detected when she enlisted as a WAVE in the Navy or at the time of re-enlistment in 1952. She had a history of infectious hepatitis in 1943. Her first prenatal visit was on May 14, 1954. Her last menstrual period had been on Jan. 25, 1954, and the estimated date of confinement was Nov. 1, 1954. She had exertional dyspnea on her first visit. Physical examination disclosed findings considered compatible with predominant mitrostenosis. A Grade 2 apical systolic murmur was audible at the apex, and a separate murmur of Grade 2 intensity was heard in the aortic valve area. No evidence of left ventricular enlargement could be demonstrated. A mitral commissurotomy was performed on July 1, 1954, during the twenty-second week of gestation. She was discharged on the thirteenth postoperative day following an uneventful recovery. She had slight vaginal bleeding and passed some clots per vaginam from Aug. 13 to Aug. 17, 1954. She was kept at bed rest and given massive doses of stilbestrol. She went into active labor on Aug. 30, 1954, and was spontaneously delivered of a 2 pound, 6½ ounce male at 31 weeks' gestation. The infant died in 5 days and the autopsy revealed: (1) lung congestion with multiple peripheral abscesses bilaterally; (2) patent ductus arteriosis; and (3) patent foramen ovale. The mother's course was uneventful until Nov. 12, 1954, when she was admitted with the diagnosis of pneumonia, left lower lobe. She showed signs of mild decompensation at this time. She was treated with antibiotics and bed rest and was discharged recovered on Nov. 19, 1954. Late follow-up examination shows her heart to be fully compensated, without enlargement, and she is working.

CASE 7.—B. R., aged 25, had a history of "joint pains" for many years but no definite attacks of rheumatic fever. She had an uneventful pregnancy and a spontaneous delivery of a 7 pound, 8 ounce female infant after an hour of labor on July 1, 1948. In 1952 she was told during a pre-employment physical examination that she had a murmur and had had rheumatic fever. During the year prior to admission she had noted orthopnea and increasing exertional dyspnea. She was first seen in the prenatal clinic on April 29, 1954, and was found to be in mild decompensation at that time. She was admitted on May 4, 1954, and a diagnosis of mitral stenosis established. She was placed on a restricted sodium intake and was digitalized. Her last menstrual period was Dec. 2, 1953, and the estimated date of confinement was Sept. 11, 1954. Mitral commissurotomy was done on May 20, 1954, during the twenty-fourth week of gestation. Five days postoperatively the patient developed pyelitis. She was treated with Gantrisin* and bed rest and was discharged completely recovered on June 22, 1954. On Sept. 1, 1954, she was readmitted to the hospital for rest prior to delivery. Labor began spontaneously and she was delivered of a 6 pound, 13 ounce female infant by outlet forceps under pudendal block anesthesia on Sept. 24, 1954. The postpartum course was completely uneventful.

CASE 8.—M. J., a 35-year-old Caucasian woman, had a history of painful, swollen joints as a child. In 1938, at the age of 18, she was hospitalized at bed rest for 3 months, followed by bed rest for 6 months. At that time a diagnosis of mitral stenosis was initially made. Three subsequent pregnancies ensued: in 1942, the spontaneous delivery of a 9 pound male infant without complications, with a 6 hour labor; in 1947, the spontaneous delivery of a 7 pound male infant without complications, with a 6 hour labor; and in 1949, the spontaneous delivery of an 8 pound male from breech presentation with a 5 hour labor.

*Wide-spectrum sulfonamide, Roche Laboratories, Division of Hoffmann-La Roche, Inc., Nutley, N. J.

This patient was first seen in the prenatal clinic in early congestive cardiac failure and was admitted to the hospital on July 2, 1955. The last menstrual period had been on Jan. 26, 1955, and the estimated date of confinement was Nov. 22, 1955. The course of treatment was absolute bed rest, digitalization, and administration of diuretics. This was the twenty-third week of gestation. She was discharged on July 8, 1955, with the decision to treat her cardiac condition conservatively during her pregnancy. She was readmitted on July 23, 1955, with tachycardia of 140 and exertional dyspnea and edema. The antistreptolysin titer was 1:50 on July 30, 1955. C-reactive protein on July 25 was 1 plus. On Aug. 24, 1955, in the twenty-ninth week of gestation, a mitral commissurotomy was done because of the increasing severity of symptoms. Her response was dramatic and she was discharged on Sept. 12, 1955. She was readmitted for 2 days on Sept. 21, 1955, because of bronchitis and was treated with antibiotics. She was readmitted in active labor Oct. 21, 1955, and was delivered of a 6 pound, 12 ounce female child by assisted breech without anesthesia. The patient's postpartum course was uneventful. The baby was a Mongoloid. Late follow-up finds the mother in good health, without cardiac enlargement or significant limitation of activity.

Selection of Cases for Surgical Correction of Cardiac Disease

The most common lesion of the heart associated with pregnancy is rheumatic mitral stenosis. The aim of mitral commissurotomy is to reduce or remove the obstruction to the blood flow imposed by the diseased valve, without creating incompetence or regurgitation. For the patient to be a candidate for surgery in pregnancy, she must have a lesion so incapacitating that its correction is imperative enough to warrant the risk. The valvular lesion must be of a type amenable to operation, and the stenosis must be the cause of enough of the patient's disability that its correction will result in a definite upgrading of her cardiac classification.

The diagnosis of rheumatic mitral stenosis in the pregnant patient does not significantly differ from that in the nonpregnant state. A history of one or more of the components of the rheumatic diathesis is present in about two thirds of patients. In many instances the patient has known mitral valvular disease prior to pregnancy and the obstetrician will be asked to follow the patient in close conjunction with the referring internist.

The ease of clinical diagnosis is usually a function of the degree of mitral valvular compromise. In a tight, long-standing stenosis, inspection and palpation will disclose an apical diastolic thrill, pulmonary closure "tap" over the pulmonary valve area, and a diffuse right ventricular "heave" along the left sternal border. Auscultation characteristically reveals a "booming" mitral first sound, a long, low-pitched diastolic rumble at the cardiac apex with marked presystolic accentuation, and an intensified and reduplicated pulmonary second sound. In early diastole the trained examiner can often separate the "opening snap" of the mitral valve from this galaxy of diastolic sounds. A high-frequency, decrescendo diastolic murmur of pulmonary insufficiency (Graham Steell) murmur may be audible along the left sternal border. This murmur is difficult to differentiate from the decrescendo murmur of aortic regurgitation. Its identification is often dependent upon the absence of peripheral signs of aortic insufficiency, i.e., left ventricular enlargement, wide pulse pressure, capillary pulse, etc. In pregnancy this important differentiation may well be an aggravating one, as the physical signs of left ventricular enlargement and decreased peripheral resistance may, in degree, be mimicked by the hemodynamic changes of pregnancy. This has great prognostic importance as the patient with dynamic aortic regurgitation can expect a poor late result following mitral valvulotomy.

Laboratory evidence may assist in the diagnosis of tight mitral stenosis. Fluoroscopy will reveal an enlarged left atrium presenting a double contour on the right and displacing posteriorly the barium-filled esophagus with the patient rotated into the right anterior oblique projection. The electrocardiogram may show right axis shift, first degree A-V block, and will quite regularly disclose broad, notched atrial complexes in multiple leads.

These physical and laboratory signs may be much less marked in the less severe case. Regularly, however, we may expect a "booming" mitral first sound, an apical rumble, and an intensified pulmonary second sound. When these are identified by the obstetrician, additional medical assistance is recommended.

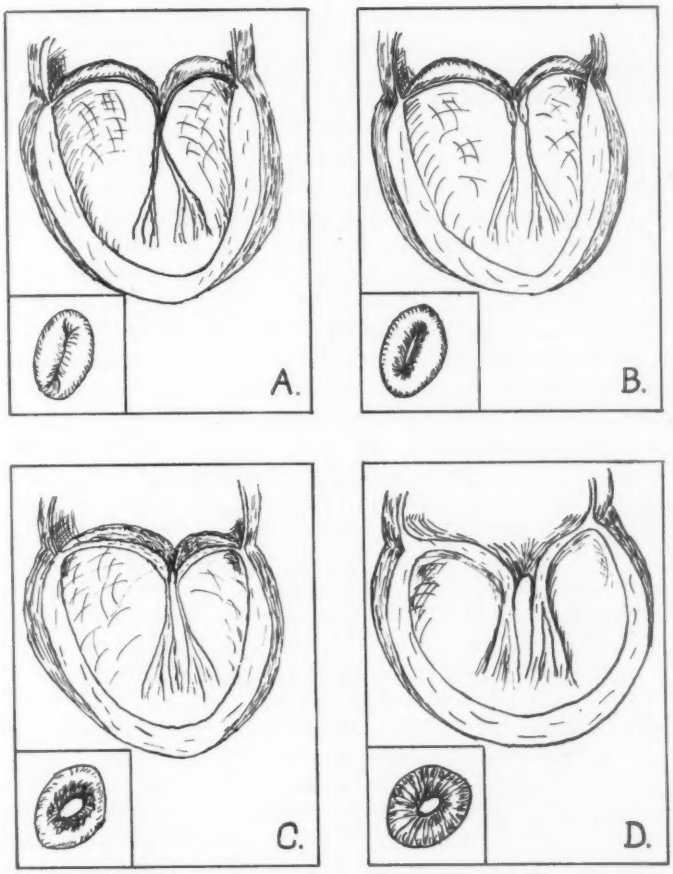

Fig. 1.—Diagram of the mitral valve in systole (insets show views from above). *A*, Normal valve. *B*, The rheumatic process has thickened the edges of the valve leaves. The main body of the cusps is unaffected, thus producing the "diaphragmatic valve." *C*, The thickening has progressed to almost the entire body of the valve leaves. The chordae tendinae and papillary muscles are still relatively normal. Regurgitation is present. *D*, The leaves, chordae tendinae, and papillary muscles are fused by extensive fibrosis, producing a completely incompetent "funnel" valve.

In the formation of mitral stenosis the active rheumatic process is followed by the deposition of fibrin and its subsequent organization on the very edge of the valve surrounding the orifice. The process of thickening at first circumscribes the orifice and then as the edge of the valve increases in size and thickness the orifice becomes smaller. At this early stage the valve leaflets are often essentially unaffected and remain pliable. During ventricular systole in such an ideal case the pliable valve leaflet is limited only

by the fibrous reaction at the orifice, and the leaflet balloons into the atrium. This "diaphragmatic" action is readily appreciated by the surgeon at his initial palpation of the valve at operation (Fig. 1, *B*). The correction of the lesion at this stage usually involves simple finger fracture of the commissures anterolaterally and posteromedially, thus creating two pliable leaves with thickened edges unattached to each other. Correction of this type of valve releases the stenosis and practically never creates a significant degree of regurgitation.

As the process of thickening extends radially (Fig. 1, *C*) the valve leaflet loses its elasticity and becomes a much less optimum valve for fracture.

If the rheumatic process becomes more extensive the cusps, chordae tendinae, and even the papillary muscles may become fused into a solid, funnel-shaped, rigid mass (Fig. 1, *D*). At this stage complicating regurgitation is nearly always present and little can be done surgically at the present level of technical ability. Such a degree of mitral stenosis is usually fibrillating, and the dense and calcific valve can be clearly seen during fluoroscopy. The "opening snap" is not audible and clinical signs of regurgitation with a harsh apical systolic murmur are usually seen.

The clinical diagnosis of coarctation of the aorta is seldom difficult. If palpation of the femoral arteries is made a part of the prenatal physical examination this lesion will not be missed. The aortic constriction leads to an elevated blood pressure in the upper extremities and a reduced pressure in the lower extremities. Collateral circulation results in large, palpable intercostal arteries, and notching of the posterior-inferior margins of several ribs. Auscultatory findings may be quite varied; however, a systolic murmur over the upper dorsal vertebrae is a common clinical finding. The chest x-ray will show, in addition to rib notching, signs of left ventricular enlargement and a small aortic knob. Occasionally poststenotic dilatation of the aorta may be identified. The electrocardiogram may show left ventricular enlargement, and the ballistocardiogram often reveals disappearance or attenuation of the K wave.

From a technical standpoint the operative procedure is not influenced by the presence of pregnancy.

Selection of Time of Operation

Transfer of the site of formation of estrogen and progesterone from ovary to placenta is probably gradual, and is completed by about the eighteenth to the twentieth week of gestation. By the fourth month the formation of the placenta is complete and the fetus is securely anchored. In view of this, it appears to be advisable to wait until after the eighteenth week to perform the operation; in our cases, however, 5 of the 8 patients were operated upon before or during the eighteenth week and none of these patients had abortions. One mother died during operation. All patients are supported by progestational hormone therapy and sedation just prior to, and following, operation.

Rose and his associates[24] have recently reported studies of the hemodynamics of normal pregnancy as measured by cardiac catheterization. Their study shows that there is an increase in cardiac output at rest observed in the earliest period of gestation studied (14 to 24 weeks). The cardiac output reaches a maximum 40 per cent increase over that of the nonpregnant control woman during the twenty-fifth to the twenty-seventh week of pregnancy, then decreases to normal just prior to term. From this it appears that, if a patient is carried successfully through the twenty-seventh week of pregnancy on

general supportive therapy, the chances of decompensation developing are lessened and she should be able to continue pregnancy without difficulty. The maximum increased cardiac output of 40 per cent measured at rest does not very well support Gorenberg and Chesley's[22] views that the "burden of pregnancy need not be feared" when treated with complete bed rest.

The work of Rose and others[24] has contributed invaluable information concerning the normal hemodynamics of the pregnant patient. By understanding these normals one can better detect and understand the process of failure or decompensation in the pregnant cardiac patient. Although cardiac catheterization is now considered a safe procedure, some cases of fibrillation following this maneuver have been reported in normal individuals. The procedure also exposes the patient and fetus to considerable radiation. Rose and his group did not feel that the normal pregnant individual should be subjected to more than one catheterization. When the cardiac patient is under the close observation of a qualified cardiologist as well as an obstetrician, cardiac catheterization seldom reveals enough additional diagnostic information to warrant the risk of the procedure. Its use is best confined to the rare congenital lesions that cannot be diagnosed otherwise.

Cardiac surgery should not, in any way, take the place of well-established, conservative measures in the treatment of the cardiac patient. If the patient, however, fails to respond to the usual treatment of absolute rest, sodium restriction, diuretics, and digitalization, and her cardiac lesion is considered amenable to surgery, then certainly surgical correction should be considered. Operation may be done at any time that an upgrading of the cardiac status is imperative enough to warrant the risk. This is where complete cooperation and coordination of the team of obstetrician, cardiologist, and surgeon become paramount.

Certainly, if the cardiac lesion is amenable to surgery, therapeutic abortion in such cases is no longer indicated.

Obstetrical Management

All prenatal patients when first seen in our clinic are examined carefully to detect the presence of any organic heart disease. If symptoms of heart disease are found and findings on physical examination confirm the original impression, the patient is then referred to the cardiologist for an evaluation of her cardiac status and an opinion concerning her ability to withstand successfully the additional burden on her heart produced by the pregnancy. When a diagnosis is established and a functional classification is made, the patient is then followed jointly by the cardiologist and obstetrician for the remainder of her prenatal course.

All patients with Class I and Class II heart disease are considered to be "favorable" and are seen twice monthly by the Abnormality Prenatal Clinic and Cardiology Service. They are evaluated closely for any abnormal weight gain or the presence of an upper respiratory infection. If the latter develops the patient is routinely hospitalized and treated energetically with antibiotics and supportive care. All Class I and II cardiac patients are placed on a sodium-poor diet and are urged to obtain 10 hours of rest per day. They are allowed to go into labor spontaneously and are given antibiotics throughout labor, delivery, and the puerperium. Delivery is accomplished under pudendal block with low forceps and episiotomy, and an effort is made to eliminate the second stage of labor as much as practicable. This type of cardiac patient ordinarily remains in bed after delivery for 3 to 5 days and may be discharged on the seventh to the tenth day.

Class III and IV cardiac patients do not undergo the predictable burden of pregnancy with any assurance of not going into failure, and special care is exercised in the handling of each case. All such patients are seen by the Cardiology Service when first encountered in the Prenatal Clinic and following classification in accordance with the New York Heart Association Classification are then seen by the Abnormality Prenatal Clinic staff. If the patient concerned is in a class denoting extreme intolerance to ordinary activity, she is hospitalized at complete bed rest for the remainder of the pregnancy. A history of previous failure or the presence of auricular fibrillation on physical examination are indications for complete rest in the hospital until term. Certain Class III patients may be treated as outpatients if they adhere strictly to the plan of management as presented for Class I and II patients but are to be hospitalized at the first indication of failing cardiac reserve and certainly prior to reaching the peak load of pregnancy. In certain instances our Class III patients may be placed at bed rest at home until the peak load has been successfully negotiated, but the majority are hospitalized, as expense plays a minor part in arriving at this decision in our institution.

The "unfavorable" cardiac patients are allowed to go into labor spontaneously and are delivered by low forceps and episiotomy under pudendal block anesthesia without the addition of epinephrine to the anesthetic agent used. These patients are kept at bed rest during the puerperium for 5 to 10 days and are usually ready for discharge 2 weeks post delivery.

Cesarean section is performed only for purely obstetrical indications but may be resorted to in some instances where labor is unduly prolonged in the elderly primigravida.

If the cardiologist feels that all the necessary findings to warrant the performance of a commissurotomy are present and this recommendation is concurred in by the Obstetrical Division and Thoracic Surgery Service, it is felt at this institution that pregnancy is no contraindication to the operation if done prior to the twenty-eighth week of gestation.

In the cardiac patient on whom commissurotomy and/or resection of a coarctation have been performed, the obstetrical management is still dependent upon the functional classification as determined by the cardiologist and is not influenced directly by the surgical procedure.

Summary

During the 4 year period from 1953 to 1956, inclusive, there have been 39 cardiac operations performed on female patients over the age of 15 years at the United States Naval Hospital, San Diego, California. Twelve of these patients were nulligravidas and are not included further in the study. There were a total of 62 pregnancies in the remaining 27 patients studied. Prior to operation there had been a total of 38 full-term deliveries; one of the infants was a Mongoloid and did not survive. There were no therapeutic abortions before operation in any of the 27 cases. There had been 13 abortions, 9 of which were in one patient, but none were therapeutically induced. One patient had one delivery followed by a commissurotomy. She subsequently became pregnant and went into severe cardiac failure prior to the third month of gestation, so therapeutic abortion and tubal ligation were performed. Seventy per cent of the 27 patients in this report showed marked improvement

of the cardiac symptoms after operation and only 2 showed no improvement. Four suffered from embolic phenomena following operation. There were 3 deaths resulting in an operative mortality of 11 per cent.

Eight of the patients were pregnant at the time of operation. Two had coarctations of the aorta. Both of these were delivered of viable term infants without difficulty following surgical repair of the lesion. One has since undergone an uncomplicated pregnancy. Six of the patients had mitral commissurotomies for stenosis. One died during operation. One was delivered of a premature infant at 31 weeks' gestation (9 weeks following operation). This infant died and was found at autopsy to have had numerous congenital anomalies. One Mongoloid infant was delivered at term. Three patients were delivered of normal term infants subsequent to their operations.

Conclusions

From an analysis of the foregoing report the following conclusions seem justified:

1. Certain selected cases of mitral stenosis and most coarctations of the aorta can be successfully surgically repaired with a minimum of morbidity and an acceptable mortality rate in the gravid woman.

2. The operation is best performed on the pregnant woman prior to the twenty-eighth week of gestation in order to escape the peak load of pregnancy.

3. Mitral commissurotomy is indicated in all Class III and Class IV pregnant cardiac patients who are being considered for interruption of pregnancy on the basis of failing cardiac reserve, provided the valvular lesion is considered amenable to surgical correction.

4. Pregnancy is not considered a contraindication to operation on the heart or great vessels if performed prior to the twenty-eighth week of gestation.

5. Cardiac surgery does not appear to affect the fetus adversely or to increase the incidence of prematurity if performed prior to the twenty-eighth week of gestation under the protective influence of progestational hormone therapy.

6. Therapeutic abortion as a means of terminating a pregnancy on the basis of mitral stenosis is rapidly becoming an obsolete method of management as a result of the successful utilization of mitral commissurotomy in indicated cases and good conservative management in the remainder.

7. In view of the definite improvement that can be anticipated from a mitral valvulotomy, tubal ligation is no longer indicated in any case requiring therapeutic abortion on the basis of cardiac failure due to mitral heart disease.

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RUPTURE OF THE SPLEEN IN PREGNANCY

Report of Two Cases and Review of the Literature

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(From Baylor University Hospital)

RUPTURE of the spleen during pregnancy or the puerperium has been reported in 42 patients.. In a few of these rupture has resulted from severe injury, pre-existing abnormality of the spleen, or a combination of the two. More often, however, a history of significant injury or of antecedent disease of the spleen has been lacking. While the cause has not been established, the number of reported cases is sufficient to suggest that pregnancy itself may predispose to rupture, especially during the last trimester.

Rupture of the spleen in pregnancy was first described by Saxtorph[60] in 1803. By 1880, 9 such cases had been reported, in all of which the diagnosis was established at necropsy. Splenectomy was first performed for this condition by Savor[59] in 1898. The patient survived and was delivered of a full-term healthy infant 3½ months later. A review of the subject first appeared in 1930, when Kotschnew and Manenkow[43] collected 14 cases from the literature and added one of their own. More recently, excellent reviews have been published by Barnett[7] and by Moore.[52] Each of these authors included tabulations of all cases known to him. To date, however, each reviewer has overlooked one or more of the reported cases,* and has omitted detailed information concerning infant mortality. In the present study an attempt will be made to complete the tabulation of all cases reported to date, and to add all available information concerning infant survival. In addition, the forty-third and forty-fourth reports of this condition will be presented, and the factors which may lead to rupture of the spleen in pregnancy will be reviewed.

A chronological outline of all known reported cases of rupture of the spleen during pregnancy, labor, or the puerperium is presented in Table I. The cases herein reported for the first time are included in this tabulation, and in all analyses of data which follow. All known reports, however brief, have been included; the lack of detailed information is indicated by question marks in the tabulation.

*The case described by Whitney[73] in 1869, the first to be reported in America, has been omitted from all reviews. The fragmentary reports of Kehrer,[37] and of Klotz[41] in discussion of Kehrer, have not been included in contemporary tabulations. The cases reported separately by von Hoch[71] and by Sommer[67] have been listed in all tabulations as separate patients; detailed perusal of these two reports indicates, however, that the authors were describing the same patient. McElin and Mussey[50] cited Fournier and Forster[24] as having reported a case of rupture of the spleen in pregnancy, but Fournier's description indicates that their patient was not pregnant. Hunter and Shoemaker[38] cite Kobak[42] as having described a case of rupture of the spleen in pregnancy, but Kobak's patient was proved at operation not to be pregnant. Hubbard[32] of New York has been referred to in some of the German references as "Hubhart," and this modification has been carried over into some of the English reviews.

TABLE I. REPORTED CASES OF RUPTURE OF THE SPLEEN IN PREGNANCY OR THE PUERPERIUM

AUTHOR	DATE	AGE	PARITY	TERM	TOXEMIA OR DISEASE OF SPLEEN	TRAUMA	FATE OF MOTHER	FATE OF CHILD	TREATMENT AND RESULT
1. Saxtorph[60]	1803	?	?	?	?	?	Died	?	Autopsy diagnosis. Death during puerperium
2. Simpson[64]	1866	?	?	6-7 months	?	?	Died	?	Autopsy diagnosis. Fragmentary report
3. Simpson[64]	1866	?	?	Post partum	?	Equivocal	Died	?	Autopsy diagnosis. Fragmentary report
4. Simpson[64]	1866	?	?	Term	?	?	Died	?	Autopsy diagnosis. Fragmentary report
5. Wilson[75]	1866	?	?	Post partum	?	?	Died	?	Autopsy diagnosis. Fragmentary report
6. Sidey[63]	1866	?	?	?	?	Equivocal	Died	?	Autopsy diagnosis. Fragmentary report
7. Whitney[73]	1869	34	Gr. ix	8 months	Toxemia	No	Died	Died	Edema of face one week. Abdominal pain, convulsions, death in 5 hours. Autopsy
8. Hubbard[32]	1879	28	?	Post partum	Malaria	No	Died	Lived	Autopsy diagnosis. Bleeding first apparent 6-8 hours after delivery
9. Schwing[61]	1880	35	P. v	9 months	?	No	Died	Died	Autopsy diagnosis. Postmortem cesarean section; dead fetus
10. Savor[59]	1898	31	P. v	5½ months	Old abscess	Yes	Lived	Lived	Splenectomy in 12-18 hours. Normal delivery 3½ months later
11. Le Lorier[44]	1905	?	?	5½ months	?	No	Died	Died	Laparotomy; source of bleeding not detected. Died; autopsy
12. Gemmell[26]	1912	31	P. ii	8 weeks	No	No	Died	Died	Splenectomy in 11 days. Died 2 days after operation
13. Martyn[48]	1913	30	P. iii	3 months	No	No	Died	Died	Laparotomy same day; bleeding source not detected; packed. Aborted and died in 2 days
14. Kehrer[37]	1921	?	?	?	?	?	?	?	Reported by title only
15. Klotz[41]	1921	?	?	?	?	?	?	?	Fragmentary report
16. Stretton[68]	1926	37	?	5 months	No	Equivocal	Lived	?	Splenectomy in 12 hours. Outcome of pregnancy not described
17. Iwantschenko[35]	1928	38	Multip.	9 months	No	Yes	Lived	Died	Splenectomy in 9 hours. Child stillborn 2 hours after operation
18. Kotschnew and Manenkow[43]	1930	20	Gr. i	Term	No	No	Died	Died	Admitted for mild abdominal pain. Fourth day, shock and sudden death. No operation
19. Bohler[11]	1931	35	?	7 months	No	Yes	Lived	?	Splenectomy and cesarean section in 36 hours. Fate of child not stated
20. Smith et al.[65]	1933	31	?	3 months	No	No	Lived	Lived	Splenectomy in 2-3 days. Normal delivery 6 months later
21. Burnett and McMenemey[13]	1935	43	P. xvi	38 weeks	No	Equivocal	Lived	Lived	Splenectomy and cesarean section in 24 hours
22. Sommer,[67] von Hoch[71] (2 reports)	1938	?	Gr. v	Term, labor	No	No	Lived	2 died	Splenectomy and cesarean section. Twins, one stillborn; the other died soon
23. Asteriades[5]	1939	25	P. ii	Term, labor	Malaria	No	Lived	Lived	Splenectomy (2 incisions). Child born vaginally during laparotomy
24. Asteriades[5]	1939	?	Multip.	7½ months	Malaria	Yes	Lived	Died	Splenectomy; postoperatively acute ma-

24. Asteriades[5]	1939	?	Multip.	7½ months	Malaria	Yes	Lived	Died	Splenectomy; postoperatively acute malaria with premature stillbirth
25. Shannon[62]	1940	34	Gr. vi	7 months, labor	Toxemia	No	Died	Died	No operation. Premature stillbirth; shock; death. Visceral hemorrhages
26. Ireneus et al.[34]	1945	37	?	Term	No	Equivocal	Lived	Died	Splenectomy in 9 days. Stillbirth 32 hours postoperatively
27. Conforth and Carangelo[17]	1946	30	Gr. vi	38 weeks	Toxemia	No	Died	Died	No operation. Admitted for severe toxemia. Died suddenly 17 days later
28. Harper and Huertas[29]	1950	20	P. i	Term, labor	No	No	Died	Died	No operation. Died shortly after low forceps delivery of stillborn infant
29. Gorman and Rowe[27]	1951	29	Gr. vi	Term	No	No	Lived	Died	Stillbirth day after onset. Splenectomy on following day
30. Barnett[7]	1952	37	P. iii	37 weeks	No	No	Lived	Died	Splenectomy and cesarean section in 18 hours. Stillborn fetus
31. King and Wigley[38]	1953	27	?	29 weeks	Toxemia	No	Lived	Died	Admitted for toxemia. Rupture in hospital. Splenectomy in 4 hours. Postoperative stillbirth
32. Marshall[47]	1953	?	?	26 weeks	?	?	Lived	?	Fragmentary report. Laparotomy and probable splenectomy. Subsequent toxemia?
33. Eastman[22]	1953	?	?	Labor	?	?	Died	?	Fragmentary report. Laparotomy, bleeding source not found. Died; autopsy
34. Anonymous (Maryland)[2]	1955	42	Gr. ix	38 weeks	No	Equivocal	Lived	Lived	Splenectomy and cesarean section in 14 hours
35. Lyons et al.[46]	1955	28	Gr. iv	6 months	No	Yes	Lived	Lived	Splenectomy in 3 days. Term spontaneous delivery 3 months later
36. Bayer[8]	1956	35	?	2½-3 months	Banti's syndrome	Equivocal	Lived	Lived	Splenectomy same day. Term spontaneous delivery 6½ months later
37. Bengel[9]	1956	38	Gr. vi	6-7 months	No	Equivocal	Lived	Died	Splenectomy same day. Child died in utero postoperatively
38. Moore[52]	1956	31	Gr. vi	35 weeks	No	Equivocal	Lived	Lived	Splenectomy same day. Term spontaneous delivery 6 weeks later
39. Moore[52]	1956	29	Gr. ii	34 weeks	No	No	Lived	Died	Splenectomy and cesarean section 24 hours (2 incisions); 4 pound infant died in 30 hours
40. Moore[52]	1956	27	Gr. iii	32 weeks	No	No	Died	Died	Splenectomy same day. Postoperative hemorrhage; death. Postmortem section; stillborn infant
41. Moore[52]	1956	24	Gr. iii	38 weeks	No	No	Died	Lived	Laparotomy 8 days after section. Bleeding source not found. Died on twenty-ninth postoperative day
42. Hunter and Shoemaker[33]	1957	?	Gr. i	39 weeks	No	Equivocal	Lived	Lived	Splenectomy and cesarean section 9 hours after onset
43. Sparkman		32	Gr. vii	37-38 weeks	No	No	Lived	Lived	Splenectomy and cesarean section 2 hours after onset
44. Sparkman		24	Gr. ii	30 weeks	No	Yes	Lived	Lived	Splenectomy 1½ hours after injury. Term spontaneous delivery 11 weeks later

CASE 1.*—Mrs. M. M., aged 32, para vi, gravida vii, type O, Rh positive, had her last menstrual period on June 1, 1955; the expected date of delivery was March 17, 1956. The antenatal course had been entirely normal with no evidence of toxemia. Her other pregnancies had resulted in spontaneous term deliveries of healthy infants, 4 of whom weighed over 9 pounds at birth.

At 7:30 P.M., on the evening of Feb. 20, 1956, at about the thirty-seventh week of pregnancy, she had just finished bathing her children when she experienced sudden severe pain in the left shoulder. This quickly spread to involve the entire abdomen, and was followed by the rapid development of severe vascular collapse. A physician who lived next door was at her bedside within 5 minutes, and her obstetrician arrived shortly thereafter. By then her pulse rate was 120, blood pressure 80/30, and her condition was deteriorating so rapidly that her physicians feared that she would die before she could be moved to the hospital.

She was transported to the hospital by ambulance and was taken directly to the operating room. Upon arrival her pulse rate had risen to 140 and the blood pressure had further declined to 70/0. An infusion of dextrose in lactated Ringer's solution was started, and was shortly followed by the administration of type O, Rh-negative whole blood of low agglutinin titer, without waiting for cross-match.

The abdomen was opened through a vertical lower midline incision. The peritoneal cavity contained a huge quantity of blood, which appeared to be coming from the left upper abdomen. Classical cesarean section was performed with the dual objective of attempting to save the infant and of allowing access to the upper abdomen. A male infant weighing 7 pounds was delivered from vertex presentation, left occipitoanterior. Initially he did not breathe, but responded satisfactorily to resuscitation after an interval of 2 or 3 minutes.

The incision was rapidly extended upward and to the left, after which it was possible to ascertain that the source of the hemorrhage was a rupture of the spleen. The spleen was detached from its points of fixation and brought down to allow manual compression of its pedicle. Thereafter the condition of the patient improved progressively and it was possible to complete the splenectomy without further incident. During the procedure the patient received 2,000 ml. of whole blood and 1,000 ml. of 5 per cent dextrose in lactated Ringer's solution. The procedure was completed at 10:45 P.M., 3 hours and 15 minutes after the initial symptoms. At the close of the operation the pulse rate was 100 and blood pressure 140/80. Additional whole blood was given during the first 8 hours after operation. In all, 3,000 ml. of blood was administered.

The spleen weighed 250 grams and exhibited a large deep tear on the lateral surface. Microscopic examination disclosed nothing of additional significance.

Except for mild atelectasis with fever on the second, third, and fourth postoperative days, subsequent convalescence was without incident. No further blood was given after the first day. The patient left the hospital on February 29, nine days after admission and operation.

An effort was made subsequently to elicit a history of trauma sufficient to account for rupture of the spleen. Initially the patient was unable to recall any incident which might have been significant. Eventually, however, she remembered that approximately 3 weeks before, while she was seated on a low coffee table, one of the children had jumped on her lap, whereupon one leg of the table broke, causing the mother to fall to the floor in a sitting position. She suffered no discomfort at that time, and was not impressed by the incident. The significance of this episode with relation to the subsequent rupture of the spleen is conjectural. The mother and child continue to enjoy good health at this time.

CASE 2.†—Mrs. C. A., aged 24, para 0, gravida ii, had her last menstrual period on Jan. 11, 1956. The expected date of delivery was March 1, 1958. The duration of preg-

*This case is reported with the permission of Dr. W. F. Guerriero and Dr. J. Wolfram.
†This case is reported with the permission of Dr. W. P. Devereux and Dr. H. T. Hayes.

nancy was estimated at 30 weeks at the time of injury. Her antenatal course had been normal. Her one previous pregnancy had terminated in a spontaneous abortion 2 years previously.

At 8:00 A.M. on Dec. 19, 1957, she was involved in an automobile collision. She was riding as a passenger in the front seat, and was apparently thrown against the dashboard. The hospital emergency room was alerted by police radio, and a physician was waiting to see her upon her arrival.

The patient was conscious and showed no evidence of vascular collapse. The pulse rate was 74 and the blood pressure 90/60. There were abrasions over the region of the spleen, with pain and tenderness in the left upper abdomen and along the adjacent costal margin. The remainder of the abdomen was soft. The uterus extended above the umbilicus consistent with 30 weeks' gestation and fetal movements could be felt. A preoperative diagnosis of rupture of the spleen was made.

Operation was performed at 9:30 A.M., 90 minutes after the accident. The abdomen was opened through a left subcostal incision. The abdominal cavity contained a quantity of blood estimated at 1,500 ml. A ruptured spleen was removed, and the operation concluded without incident. The patient received 1,000 ml. of whole blood during operation and did not suffer any profound or prolonged hypotension before or during the operation. She received a third unit of blood after operation and a fourth on the following day, totaling 2,000 ml. for the entire period of hospitalization. She recovered without further incident, and was dismissed from the hospital on December 24, 5 days after injury and operation.

The pregnancy proceeded to term without complication. On March 4, 1958, 11 weeks after splenectomy, the patient had a term spontaneous delivery of a healthy male infant who weighed 7 pounds, 4 ounces.

Clinical Behavior

Rupture of the spleen in pregnancy usually occurs in multiparous women, only 3 instances having been reported in primiparas (Cases 18, 28, and 42). The majority of instances of rupture have occurred during the last trimester of pregnancy. Distribution of reported cases as to the time of their occurrence is as follows: first trimester, 4; second trimester, 4; third trimester, 29; post partum, 3; not stated, 4. Rupture is stated to have occurred during labor in 3 patients and at or near term in 13. In some of these reports it is difficult to determine whether rupture actually occurred after labor had begun, or whether precipitate premature labor ensued as a consequence of the rupture. In any case, the time of greatest susceptibility to rupture of the spleen is clearly the period immediately before, during, or just after labor. Similarly, it is notable that this is also the time of greatest susceptibility to rupture of arterial aneurysms in pregnancy, regardless of their location, and of other types of vascular rupture in both normal and toxemic pregnancies.

The symptoms of rupture of the spleen complicating pregnancy are varied, and are comparable to those which occur in the absence of pregnancy. Evidence of severe intra-abdominal hemorrhage is ordinarily the predominating feature. Abdominal pain is customarily but not always present and is usually most intense in the left flank or hypochondrium. Radiation of pain to the left shoulder is frequent but variable. The presence of a pregnancy and the frequent absence of an obvious etiological factor usually lead to confusion in diagnosis. Depending upon the stage of pregnancy in which rupture occurs, the most common preoperative diagnoses are likely to be: ruptured ectopic pregnancy; rupture of the uterus; abruptio placentae or occult intra-abdominal hemorrhage. A correct preoperative diagnosis has been made or suspected on 6 occasions (Cases 19, 26, 29, 32, 39, 44).

Of the 44 instances of rupture of the spleen in pregnancy, 16 have occurred in the United States. The geographical distribution of the remaining cases is as follows: England, 13; Germany, 7; France, 5; Russia, 2; Poland, 1; Canada, 1. Most authors have described single cases only. Exceptions to this are the reports of Moore[52] (4 cases), Simpson[64] (3 cases), Asteriades[5] (2 cases), and the present report (2 cases). Two instances of rupture occurred in Negroes (Cases 27 and 34), and the remainder in Caucasians.

Delayed Hemorrhage.—Numerous instances have been described in which an initial injury is suffered by the spleen, with or without immediate symptoms, to be followed by a latent period lasting several days, hours, or weeks, culminating in the sudden appearance of signs of renewed internal hemorrhage. The latent period is characterized by relative or complete freedom from symptoms. The initial injury often is comparatively slight. In a classic review of this condition in 1932, McIndoe[51] was able to collect 45 cases from the literature, to which he added one of his own. He proposed two explanations to account for the sequence of events in delayed hemorrhage: The first of these is frank rupture of the parenchyma and capsule of the spleen, with the development of a perisplenic hematoma between the spleen and surrounding structures; the eventual detachment of this hematoma leads to the sudden renewal of hemorrhage. The second explanation is a type of rupture which involves the parenchyma only, without a tear in the capsule. In this type of injury the initial hemorrhage is limited by its confinement within the capsule, but continues to dissect beneath it, stripping it along with some attached splenic tissue. The latent period is terminated by rupture of the capsule and the development of fresh hemorrhage. McIndoe defined delayed hemorrhage as the condition in which there was a latent period of at least 48 hours, and called attention to the parallel between this condition and ectopic pregnancy, in which delayed hemorrhage is notoriously common. By 1943 Zabinski and Harkins[78] were able to collect 179 cases of delayed rupture from the literature, including 4 of their own. This condition has recently been reviewed by Fultz and Altemeier,[25] whose report of 15 cases represents the largest personal series to have been recorded. Among the cases of rupture of the spleen in pregnancy, 4 can be classed as instances of delayed hemorrhage. In only one was there a history of injury; in the remaining 3, however, there was a latent period between the initial symptoms and the subsequent development of severe hemorrhage. These are summarized in Table II.

TABLE II. DELAYED RUPTURE OF THE SPLEEN IN PREGNANCY

AUTHOR	CASE NO.	INITIAL INJURY	INTERVAL	RESULT
Gemmell[26]	12	No injury; pain in left upper abdomen and flank with collapse	10 days	Splenectomy day after admission; 10-11 days after initial symptoms
Kotschnew and Manenkow[43]	18	No injury; hospitalized for abdominal pain and then dismissed	5 days	Died suddenly at home
Ireneus et al.[34]	26	Car accident; no apparent injury	8 days	Splenectomy 8 hours after onset of delayed symptoms
Moore[52]	41	Cesarean section followed by shoulder pain and abdominal distention; improved and dismissed	5 days	Laparotomy 8 days after section. Bleeding source not found. Died

Pathogenesis

Ruptures of the spleen in pregnancy may be divided into four categories, as follows: Those in which the rupture is associated with trauma; those

which occur in previously diseased spleens; those associated with toxemia of pregnancy; and those in which there is no evidence of trauma, pre-existing disease of the spleen, or abnormality of the pregnancy.

Trauma.—In the entire series there were 16 cases in which trauma of some degree was described (Table III). In 10 of these, however, the injury was apparently trivial and not of an extent ordinarily associated with visceral injury. In 2 instances, for example, sudden pain developed as the patient reached over her head to turn out a bed lamp. In situations in which evidences of splenic rupture develop in response to trauma which is not out of proportion to that encountered regularly in the ordinary activities of the day, it seems reasonable to consider that the trauma is an incident in the occurrence of rupture rather than a primary cause. In some of the reports in this series the traumatic factor is difficult to evaluate. In the case described by Whitney,[73] for example, there were two convulsive episodes; however, abdominal pain had already developed prior to the first convulsion. In all cases of rupture of the spleen during labor or shortly thereafter, the role of muscular contraction during delivery is a traumatic factor of conjectural significance.

TABLE III. RELATION OF TRAUMA TO RUPTURE OF THE SPLEEN IN PREGNANCY

AUTHOR	CASE NO.	DESCRIPTION OF TRAUMA
1. Simpson[64]	3	"Some unusual muscular exertion"
2. Sidey[63]	6	"An act of overstretching"
3. Savor[59]	10	"Kicked several times by a drunken man"
4. Stretton[68]	16	Coitus 2-3 hours prior to onset of symptoms
5. Iwantschenko[35]	17	Received 3 or 4 blows with a child's tub
6. Bohler[11]	19	Struck in left flank with an aluminum pot
7. Burnett[13]	21	Reached over head to turn out bed lamp (immediate pain)
8. Asteriades[5]	24	Traumatic rupture of malarial spleen; mechanism not stated
9. Ireneus[34]	26	Auto accident; no evidence of significant injury
10. Anonymous[2]	34	Reached over head to turn out bed lamp
11. Lyons et al.[46]	35	Fell down stairs
12. Bayer[8]	36	Slight injury to lumbar region 14 days before. No evidence of injury and no symptoms then or in interval
13. Bengel[9]	37	Lifted small iron stove; immediate pain
14. Moore[52]	38	Light blow to left flank while climbing off trunk. Local pain
15. Hunter and Shoemaker[33]	42	Slipped; fell; struck back on footstool; injury apparently trivial
16. Sparkman	44	Auto accident; immediate pain and tenderness over spleen

Antecedent Disease of the Spleen.—Antecedent disease of the spleen is an established factor in the pathogenesis of rupture of this organ. Rupture of the spleen, either spontaneous or in response to minimal trauma, has been described in association with malaria,[30] infectious mononucleosis,[66] subacute bacterial endocarditis,[77] typhoid fever,[18] typhus fever,[12] relapsing fever,[12] sepsis,[21] infectious hepatitis,[76] influenza,[23] Banti's syndrome,[66] tuberculosis,[49] syphilis,[49] sarcoidosis,[36] leukemia,[58] torsion,[1] hemangioma,[4] hydatid disease,[69] and amyloid disease.[49]

In the series of 44 cases of rupture of the spleen in pregnancy, 3 occurred in association with malaria (Cases 8, 23, and 24), one with Banti's syndrome (Case 36), and one in a spleen containing an old abscess (Case 10); significant trauma was also described in this latter case. In several other reports the spleen was described as showing varying degrees of enlargement; this, however, is of doubtful significance, since the ruptured spleen customarily contains a

considerable mass of blood clot. In the case reported by Conforth and Carangelo[17] thrombosis of the splenic vein is described. Their description, however, is that of a recent thrombus which may have followed the rupture rather than preceded it. Thus, of the 44 cases of rupture of the spleen in pregnancy, there are no more than 6 instances in which antecedent disease of the spleen can be regarded as a significant factor in the pathogenesis of rupture.

Rupture Associated With Toxemia of Pregnancy.—Vascular and visceral ruptures in various locations have been described in association with toxemia of pregnancy. These include intracranial[20, 72] and retroperitoneal[40] hemorrhages, rupture of the liver,[14, 28, 57, 74] and suprarenal rupture or hemorrhage.[3, 19] The factors in toxemia which may lead to vascular or visceral rupture include diffuse angiitis, hypertension, thrombosis, and parenchymatous necrosis. These ruptures characteristically occur at or near term.

In the series of 44 cases of rupture of the spleen in pregnancy, manifestations of toxemia were observed in 4 (Cases 7, 25, 27, and 31).

Rupture of the Spleen in Pregnancy, in the Absence of Trauma, Toxemia, or Known Antecedent Disease of the Spleen.—After disposal of the cases in which the etiology is more readily apparent (trauma; diseased spleen; toxemia of pregnancy), there remains a group in which no such factor is apparent. This includes the great majority of the reported cases. Several possible etiological factors have been suggested, including the following: changes in relation of intra-abdominal viscera incident to enlargement of the uterus; muscular contractions of the abdomen during parturition; changes in size of the spleen during pregnancy. Since the first two of these are a part of normal parturition, it seems unlikely that they could be significant in the absence of other contributory factors. Little information is available concerning the size of the spleen in pregnancy. Barcroft and Stevens[6] described reduction in volume of the exteriorized spleen in a small group of pregnant dogs. McElin and Mussey[50] reviewed the literature relative to the effect of function and disease of the spleen on female physiology. At the present time there is no valid evidence to suggest that change in size of the spleen per se is responsible for rupture of this organ in pregnancy. Additional factors which merit consideration include: changes in blood and plasma volume incident to pregnancy and vascular anomalies within the spleen. Each of these will be considered subsequently in greater detail.

In seeking the explanation of rupture of the spleen in pregnancy, a comparison may be drawn between this condition and the ruptures of other vessels and organs which have been described in association with otherwise normal pregnancies. This includes both the rupture of vessels apparently normal and of those in which aneurysms were subsequently demonstrated. Rupture of apparently normal uterine and ovarian vessels has been described by Kisimoto and associates[39] and by Hodgkinson[31]; in the retroperitoneal vessels by O'Connor[53] and by Kistner,[40] and in the inferior mesenteric artery by Le Souef.[45] In all the foregoing, rupture occurred in the latter portion of pregnancy. Rupture of arterial aneurysms during pregnancy has been reported with some frequency. These have recently been reviewed by Pedowitz and Perell,[55, 56] who were able to collect reports of 127 aneurysms of the aorta or its major branches (including 35 aneurysms of the splenic artery) and 79 reports of proved or probable cerebral aneurysm encountered during pregnancy. These authors stress the fact that the frequency of rupture of these aneurysms parallels the alterations in circulatory volume during pregnancy, and that a change in the hemodynamics is the most common factor predisposing to rupture of such an aneurysm. They observe that 50 per cent of

dissecting aneurysms in women under 40 have occurred during pregnancy. In discussing rupture of the spleen in pregnancy, they state that "it is possible that these represent rupture of intrasplenic aneurysms and careful dissection of the vascular network might have disclosed the presence of the responsible lesion." While this is hypothetical, it is an attractive theory, and might provide an explanation for the occasional spontaneous rupture of the spleen which occurs in the nonpregnant and apparently healthy individual. All cases of this type which have been reported have recently beeen reviewed by Orloff and Peskin.[54]

Pronounced changes in blood and plasma volume occur during pregnancy. These have been described in detail by Caton and associates,[15, 16] Tysoe,[70] Berlin and co-workers,[10] and others. There is general agreement that a pronounced increase in red-cell and plasma volume occurs during pregnancy, reaching the maximum late in the third trimester. The increment in whole-blood volume is estimated by Caton to be 45 per cent, with a 40 per cent increase in red-cell volume and a 49 per cent increase in plasma volume. It is also agreed that the volume of extravascular fluid increases up to the onset of labor. Plasma volume is thought to return to normal within 30 days after delivery, while the return of red-cell volume to normal requires approximately 2 months. During the latter weeks of pregnancy fluid apparently shifts from the plasma to the extravascular compartment, representing about 25 per cent of the previous increment in plasma volume. The great majority of cases of splenic rupture in pregnancy have occurred during the last trimester or in the puerperium (32 of 40 cases in which data are available); in 16 cases rupture has occurred at or near term. It appears, therefore, that rupture of the spleen is far more likely to occur during that phase of pregnancy in which increases in blood volume are most pronounced. The same is true of ruptures of other vessels and organs which have been described both in normal pregnancies and in those complicated by toxemia.

Summary of Pathogenic Factors.—Rupture of the spleen in pregnancy may be the result of various factors, both physiologic and pathologic. Of the physiologic factors, the increase in blood volume incident to pregnancy offers the most plausible explanation, and may explain the preponderance of ruptures late in pregnancy. The trauma of parturition may be contributory in some instances. Pathologic factors include external trauma (which may be minimal), antecedent disease of the spleen, and toxemia of pregnancy. It has also been suggested that rupture in some instances may be the result of intra-splenic arterial aneurysms, but as yet no such aneurysms have been demonstrated.

Treatment and Results

The treatment of rupture of the spleen complicating pregnancy consists of splenectomy with or without concomitant cesarean section. Of 44 reported cases, information concerning maternal survival is available in 42. Splenectomy has been performed in 25, with 2 maternal deaths, yielding a maternal mortality of 8 per cent when splenectomy is performed. In the absence of splenectomy, death has invariably occurred. Four such patients were subjected to laparotomy but the source of bleeding was not discovered (Cases 11, 13, 33, and 41). The maternal mortality for all reported cases is 45 per cent; if one considers only the last 30 years, the death rate is 26 per cent.

Specific information concerning infant survival is often lacking. On the basis of available information, however, 19 of 32 infants are known to have died, yielding a fetal mortality rate of 59 per cent. In the last 30 years 14

of 25 infants died (56 per cent). These infant mortality rates would be even higher if they were corrected by exclusion of cases in which the infant was born before symptoms of rupture of the spleen first become evident. Fetal survival is obviously closely related to the severity and duration of maternal hypotension and hypoxia, as well as to related conditions such as toxemia. The best prospect for fetal salvage is obtained by early correction and control of hemorrhage rather than by the particular choice of procedure relative to the fetus itself. Cesarean section has been performed 10 times. Two of these were postmortem sections (Cases 9 and 40), with recovery of a dead fetus in each instance. In the remaining 8 cases, 4 infants survived, 3 died, and the outcome in one was not stated. All 8 mothers survived.

Both the mother and the child survived in 11 instances (Cases 10, 20, 21, 23, 34, 35, 36, 38, 42, 43, and 44). In 4 of these splenectomy and cesarean section were performed simultaneously. In a fifth, vaginal delivery of the child occurred during splenectomy. In the remaining 6, following splenectomy, pregnancy proceeded uneventfully to term with spontaneous delivery of a living infant 6½, 6, 3½, and 3 months, and 11 and 6 weeks later.

It thus appears that pregnancy is likely to proceed without interruption if splenectomy is performed promptly or while the mother is still in good condition. When splenectomy is performed at or near term, preliminary cesarean section facilitates exposure of the spleen and offers a good chance of fetal survival.

Summary

All reported cases of rupture of the spleen in pregnancy and the puerperiuum are reviewed. Two additional instances of this condition are described, bringing the total of reported cases to 44. This complication is more common in multiparous women, and is more likely to occur in the last trimester of pregnancy.

In some instances rupture of the spleen was associated with significant trauma, antecedent disease of the spleen, or toxemia of pregnancy. In the majority of cases, however, none of these factors was present. It is therefore inferred that normal pregnancy in itself may predispose to rupture. If rupture of the spleen in pregnancy is compared with spontaneous rupture of the spleen in various diseases, it is found that pregnancy is second only to malaria in frequency of reported cases of splenic rupture.

The factors responsible for rupture of the spleen in pregnancy are not established. It is likely that a combination of factors may be responsible. A parallel may be drawn between this condition and other vascular ruptures which have been described in pregnancy. The latter category includes rupture of aneurysms of widespread distribution, rupture of vessels presumed to be normal, and rupture of vessels in subjects with toxemia of pregnancy. It is notable that vascular rupture in all these conditions occurs much more commonly during that phase of pregnancy in which increases in blood volume reach their maximum. Of the various factors which may predispose to vascular rupture in pregnancy, that of hypervolemia appears to be the most constant and the most significant. In toxemia the additional factors of hypertension and widespread angiitis are present. Finally, the hypothesis that the spleen may contain vascular anomalies such as aneurysms offers an attractive theoretical explanation for some instances of this complication.

The outstanding symptoms of rupture of the spleen in pregnancy are those of intra-abdominal hemorrhage. Correct preoperative diagnosis is rarely made, this condition usually being confused with abruptio placentae, rupture of the uterus, or rupture of an extrauterine gestation.

Maternal prognosis is good if splenectomy is performed. Without splenectomy, death has occurred in all reported cases. The fetal outcome appears to depend principally upon the length and severity of hypotension and hypoxia. When rupture of the spleen occurs early in pregnancy, the prompt performance of splenectomy is likely to allow the pregnancy to proceed normally to term. If rupture occurs in the latter part of pregnancy, the performance of cesarean section in conjunction with splenectomy enhances the exposure for splenectomy and affords a good chance of fetal survival. In the pregnant woman at or near term, the sudden development of signs of intra-abdominal hemorrhage should arouse the suspicion of rupture of the spleen.

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RUPTURE OF THE COMMON BILE DUCT AS A CAUSE OF MATERNAL DEATH

A Case Report

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THE difficulties in diagnosis of acute abdominal conditions in the last trimester of pregnancy are manifold. The importance of making the diagnosis early is well known; late operation is usually associated with high maternal and fetal mortality. This case report, while presenting an unusual abdominal catastrophe, is representative of the general problems of diagnosis and the dire results of late surgical intervention.

This was the second admission of a 35-year-old married woman, gravida vii, para vi. Her chief complaint was right upper quadrant abdominal pain. A diagnosis of chronic cholecystitis had been made in 1945 following which she had numerous attacks of cholecystitis for which operation was frequently recommended but never accepted. On June 4, 1956, she registered at the Prenatal Clinic for her seventh pregnancy; the expected date of confinement was Jan. 15, 1957. At that time she was complaining of intermittent right upper quadrant abdominal pain. She was referred to the Surgical Out-Patient Department, where she was advised to continue with conservative treatment during pregnancy and to have cholecystectomy after delivery.

She was admitted on Dec. 3, 1956, at 2 A.M. with right upper quadrant abdominal pain. She had no fever and no jaundice. The pulse was 90, the blood pressure 120/70. Abdominal examination showed tenderness to deep palpation in the right upper quadrant with muscle guarding. Most of the abdomen was occupied by the gravid uterus and was not remarkable. The fetal heartbeat was good. The surgical department advised "vigorous conservative management" and in the next few hours her condition improved.

The pain became more and more severe, however, but her general condition remained satisfactory until 6 A.M. of the following day when she began having uterine contractions. At this time the patient suddenly began vomiting dark brown material. The blood pressure dropped to 80/0; the pulse rose to 120. The abdomen was tender and rebound tenderness was present. Forced intravenous fluids, neo-synephrine and Levophed, did not improve her status. The white blood count was 32,500 with 85 per cent polymorphonuclear leukocytes. The fetal heartbeat disappeared and the uterus became spastic. At 9 A.M., since there was the possibility of abruptio placentae, an attempt was made to stimulate labor by rupturing the membranes and administering Pitocin. The alkaline phosphatase was 4.4 Bodansky units and serum amylase 120 Somogyi units (control 63). At 11:45 A.M., the patient was delivered of a stillborn infant without any effort, followed in 7 minutes by the placenta, which was normal. Vaginal blood loss during the delivery was minimal. After the delivery the patient came out of shock, the blood pressure rose to 110/80, the pulse came down to 100 (with Levophed still running).

Her condition suddenly deteriorated at 2:15 P.M., at which time the blood pressure and pulse became unobtainable. A needle paracentesis showed bile in the abdominal cavity. At

4 P.M., an exploratory laparotomy, under field-block anesthesia, revealed bile peritonitis due to perforation of the common bile duct, with 3,000 c.c. of bile in the abdominal cavity. No free gallstones were found. There was fatty necrosis scattered throughout the abdomen. The pancreas appeared normal. The patient died on the table at 6 P.M., in spite of cardiac massage, 40 hours after admission to the hospital. Culture of the bile from the peritoneal cavity was sterile. The fragment of gall bladder removed during the operation showed chronic cholecystitis and the omentum showed fatty necrosis. No autopsy was performed.

Comment

A relationship between gall bladder disease and pregnancy has always been suspected and very interesting work has been done on this subject by Biskind and Pevaroff,[1] Gerds and Boyden,[2] Gerwig and Thistlethwaite,[3] and Huggins, Harden, and Grier.[4] They have pointed out the fact that cholelithiasis is five times as common in women as in men; also, that gallstones are more frequent in women who have borne children than in those who have not. Biliary colic usually occurs in women of childbearing age and these women often begin having trouble either during pregnancy or shortly after delivery. Therefore, cholelithiasis is considered a very frequent complication of pregnancy. About one woman in 2 will have gallstones during the childbearing years. All gallstones contain cholesterol and their formation during pregnancy has been attributed to the fact that blood cholesterol increases during gestation.[2] A second factor is a definite retardation in the flow of the bile and the emptying of the gall bladder during pregnancy. This stasis has been attributed to a hormone mechanism.

Louw and Louw[5] and Alders[6] have written excellent articles concerning the "acute abdomen" in pregnancy. An acute abdominal crisis with peritonitis occurring in the last trimester of pregnancy, labor, or the puerperium is a most grave situation with a maternal mortality of about 50 per cent, and the child is usually stillborn.[5] The management of this condition is one of the most difficult surgical and obstetrical problems.

In making the differential diagnosis between attacks of colicky pain and labor pain, one should look for the absence of uterine contractions in the first case. In treating an acute abdominal crisis, it is important to perform immediate operation when indicated, regardless of the stage of pregnancy or labor. As long as the offending organ has not ruptured, the risk to the mother and to the child is minimal.

A review of the literature shows no case of rupture of the common duct associated with pregnancy. There was only one case[7] of perforation of the gall bladder with bile peritonitis, in the eighth month, treated successfully by drainage of the gall bladder, high classical cesarean section, and posterior colpotomy drainage.

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Gynecology

OBSERVATIONS ON THE BEHAVIOR OF HUMAN ENDOMETRIAL CELLS IN TISSUE CULTURE*†

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THE investigations, a brief account of which is presented here, were initiated about three and one-half years ago. They were motivated by the wish to obtain more information on the normal and malignant cytology of the human endometrium and its rather unique potentialities for proliferation, growth, and differentiation. One might indeed expect to find these qualities highly accentuated in an organ subjected to such severe losses of tissue as those occurring periodically in the endometrium throughout the entire reproductive life of a woman.

Because of its ever-changing character and its many important functions, the endometrium presents a variety of interesting problems for study. One of these is related to an observation made in our laboratory about four years ago, that of a rather specific morphologic process consisting of a mass production of phagocytic elements through the differentiation of cells exfoliating from the endometrial mucosa.[1] Its occurrence toward the end of the menstrual bleeding and the beginning of the proliferative phase is so timed as to serve the purpose of contributing to the cleansing of the uterine cavity from the menstrual detritus. It was hoped that corroborating evidence of this phenomenon might be obtained through the study of endometrial tissue in vitro.

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†Presented at the Fifth Annual Meeting of the Inter-Society Cytology Council, Augusta, Ga., Nov. 14, 1957.

Historical

Endometrial tissue has been studied in living cultures since 1926 by a number of investigators. Of these we may mention here Mayer and Heim,[2] Cron and Gey,[3] Heim,[4] Traut,[5] Caffier,[6] Hirsch and Jones,[7] Azumi,[8] Cameron,[9] Stuermer and Stein,[10] Randall, Stuermer, and Stein,[11] Keettel and Stein,[12] and Moore.[13] The viability of endometrial explants has been a point of general agreement in all these studies. Cells growing out of these were found to consist chiefly of two types of cells, some derived from the epithelial components of the tissue, and others, interpreted as fibroblasts, evidently originating in the stroma.

Variations in the rate of growth with an apparently increased rate during the proliferative phase have been noted by those who have studied cultures at various stages of the sex cycle. However, the viability of menstrual desquamates has been questioned by some of the investigators. The increased growth activity of the endometrial explants during the proliferative stage was found in some instances to be accompanied by a higher oxygen consumption.[10, 11] Tissue cultures of benign and malignant neoplasms of the endometrium were also part of the above studies. Proliferation and growth were found to be more active in these than in cultures of normal endometrial tissue.

Material

Material for this investigation consisted of specimens of human endometrial tissue obtained by aspiration, curettage, or hysterectomy, largely from patients of the Lying-In Hospital of Cornell Medical Center, through the courtesy of its Director, Dr. R. Gordon Douglas.* Thus far, cultures of 235 specimens of endometrial tissue, representative of all phases of the normal menstrual cycle and of various pathologic conditions of the uterine fundus, including benign and malignant neoplasms, have been studied. Cytologic smears and histologic sections have, in most instances, been available for comparison with corresponding living cells as seen in cultures.

Method

The Maximow double cover slip method was used throughout the study. Nutrient medium consisted of 1 part of a 50 per cent solution of chick embryo extract, 1 part fowl plasma, and 3 parts placental chord serum (human). Sodium penicillin and streptomycin calcium chloride were added to give a final concentration of 250 units of each per cubic centimeter. Two or three fragments of tissue were placed on a cover slip containing 2 drops of the above mixture. The cultures were washed in Tyrode solution every 48 hours and a fresh drop of medium was added to each culture. The majority of the cultures were kept in good condition with this technique for approximately 10 days or more. In one case cultures remained viable until the twenty-first day.

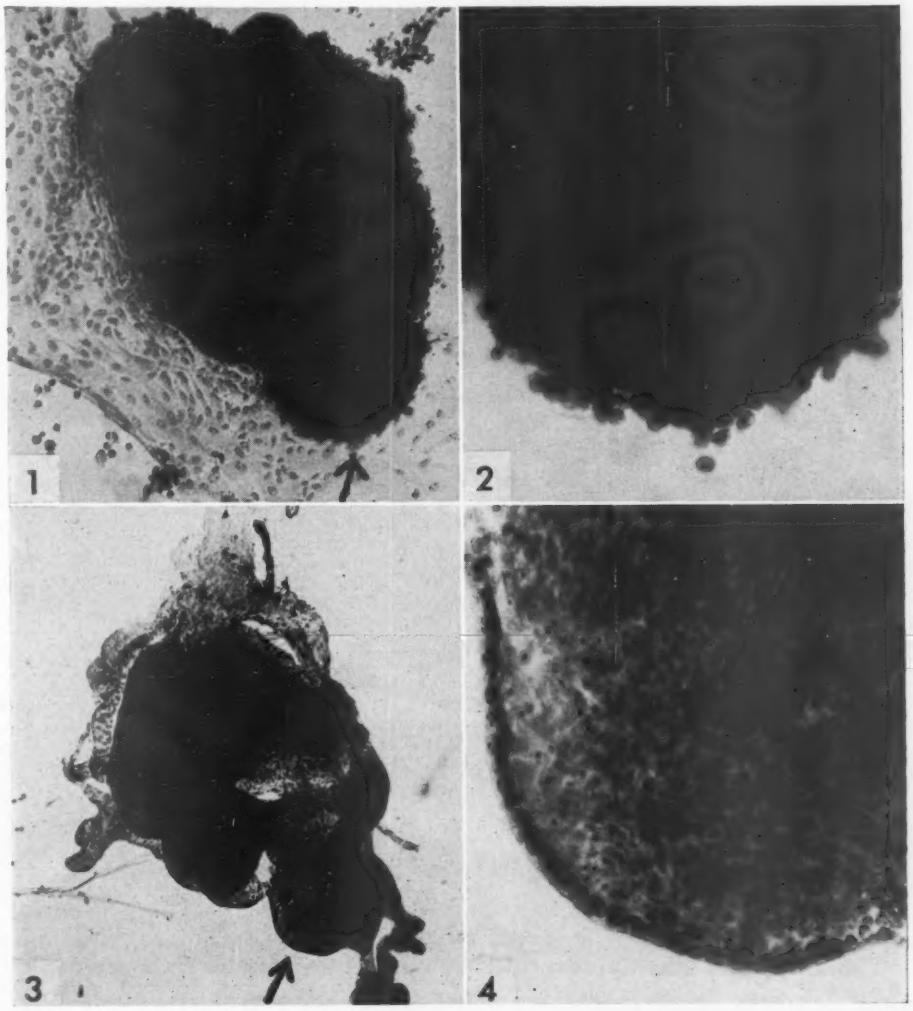
Preservation and staining of cultures for a cytologic study were as follows: The cultures were first washed in Tyrode solution for approximately 15 minutes,† then fixed in a solution of equal parts of alcohol and ether for 30 minutes to 1 hour and stained with hematoxylin and orange G in accordance with the Papanicolaou procedure.

*We wish to express our appreciation to Dr. Douglas for his cooperation in the procurement of the material as well as for the facilities and privileges extended to us in the course of these investigations.

†In order to prevent any loss of cells, the Tyrode solution is not decanted, but pipetted throughout the washing.

Observations

The report being given here is limited to a brief description and illustration of observations pertaining to some of the major points involved in our study. One of these has been the difference in the behavior of explanted endometrial tissue during the various phases of the normal menstrual cycle. Our findings are in agreement with those of previous investigators who observed marked growth activity in all endometrial explants but a maximum growth potential pre-eminently during the proliferative phase. From the morphologic point of view it is of interest that cyclic variations are noticeable also in the structural pattern and the type of growth of the explants.

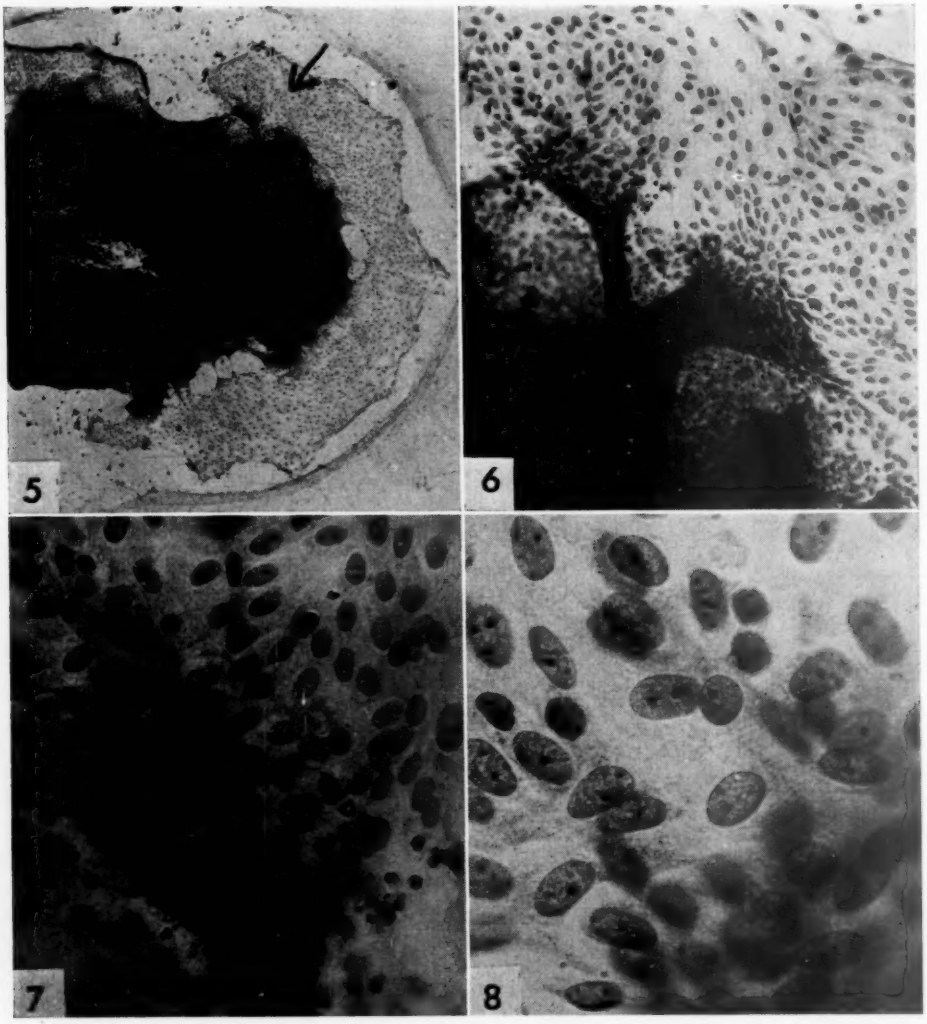


Figs. 1 and 2.—Endometrial tissue culture during proliferative phase. (Fig. 1, ×100. Fig. 2, ×300.)
Figs. 3 and 4.—Endometrial tissue culture during secretory phase. (Fig. 3, ×50. Fig. 4, ×300.)

Fig. 1 shows an endometrial cell cluster from a sixth-day culture illustrating the proliferative pattern. The specimen was obtained by endometrial aspiration from a clinic patient 45 years old, on the eleventh day of the menstrual cycle. The lighter cells adjacent to the cluster are epithelial cells which have grown out of the explant.

Fig. 2 shows, at a higher magnification, the outgrowth from the surface of the explant. Note the detachment of some of the superficial cells.

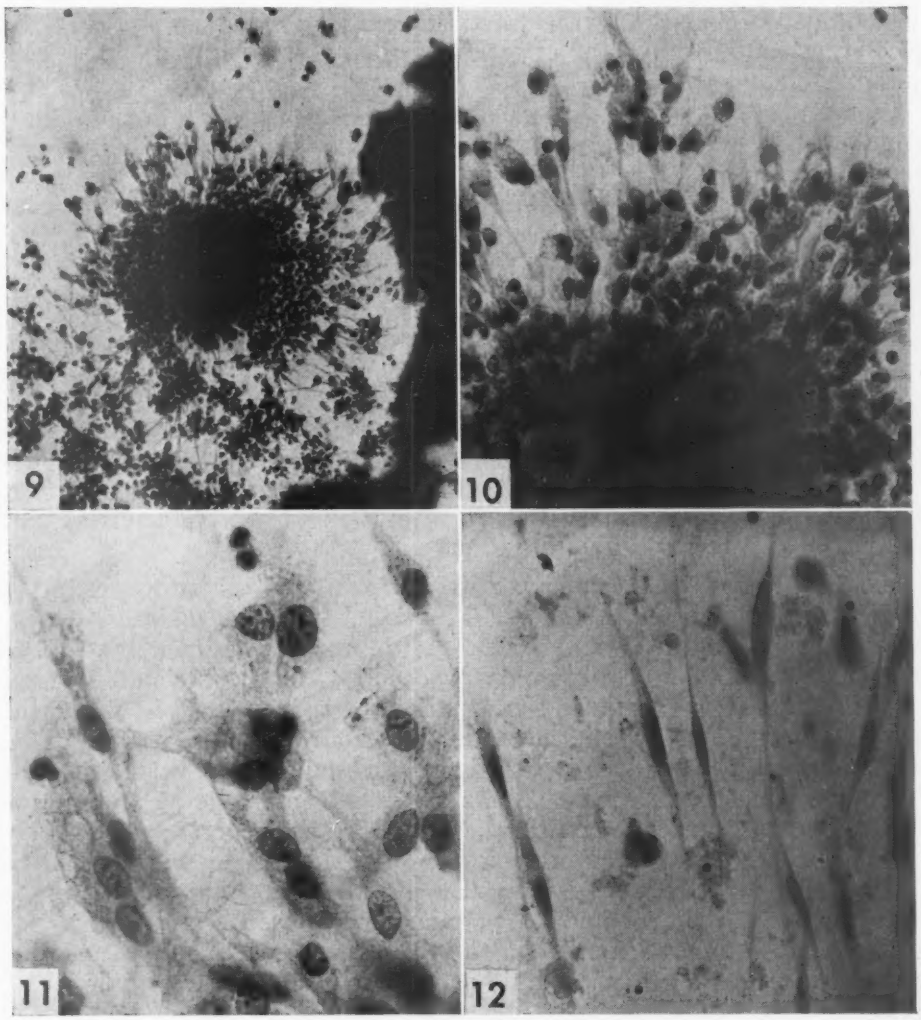
Fig. 3 shows an endometrial explant from a tenth-day culture. The specimen was obtained at a diagnostic curettage from a patient 44 years of age on the twenty-third day of the menstrual cycle, i.e., during the secretory phase. A higher magnification from an area of the surface of this explant is illustrated in Fig. 4. Note the presence of a well-differentiated epithelial lining. No outgrowth of cells could, of course, be expected from such an area.



Figs. 5-8.—Endometrial tissue culture during proliferative phase, demonstrating extrusion of epithelial cells from gland openings. (Fig. 5, ×25. Fig. 6, ×100. Fig. 7, ×300. Fig. 8, ×600.)

When a culture is examined under low magnification, a false impression of a cellular outgrowth from an epithelialized area may sometimes be gained, but this can, as a rule, be readily corrected by a sharp focusing under high magnification. Where then do all these cells, which are so frequently bordering epithelialized areas, come from? An answer to this question may be offered

by the case illustrated in Figs. 5 to 8. Fig. 5 shows a fifth-day endometrial tissue culture obtained by aspiration from a clinic patient 43 years of age on the eighth day of the menstrual cycle. On close inspection of this explant, which is practically surrounded by outgrowing epithelial cells, one can see a rich outflow of such cells from a number of open glands. This is shown more distinctly in Figs. 6 to 8 taken at a higher magnification. Inasmuch as fragmented glands may be expected to be found in most explants, one might surmise that numerous viable cells may be coming out from their open ends.



Figs. 9-12.—Endometrial tissue culture during proliferative phase, exhibiting elongated cells which are presumably stromal in origin. (Fig. 9, ×100. Fig. 10, ×300. Fig. 11, ×600. Fig. 12, ×300.)

As already stated, practically all students of endometrial tissue in vitro have noted two basic varieties of outgrowing cells, epithelial, which normally appear as round or polygonal cells in sheetlike formation (as seen in Figs. 6 to 8) and other, markedly elongated cells which have generally been interpreted as fibroblasts. Cells of the second variety are shown under low,

medium, and high magnifications in Figs. 9 to 11. These are photomicrographs of a 48 hour culture prepared from a specimen obtained at a hysterectomy preceded by a curettage.* The operation was performed on the ninth day of the cycle for a myoma of the uterus. It is evident that the cluster from which these elongated cells are derived consists exclusively of stromal cells without any trace of epithelial tissue. Cells exhibiting extreme elongation, as shown in Fig. 12, have been observed in some of our cultures, mainly during the proliferative phase. The cells illustrated in Fig. 12 are from a specimen obtained from a woman 42 years of age operated upon on the seventh day of the menstrual cycle. Since, during the proliferative phase, the endometrial mucosa undergoes marked vascularization, it is difficult to decide whether these fibrous cells, which are apparently of stromal origin, represent fibroblastic or endothelial elements.

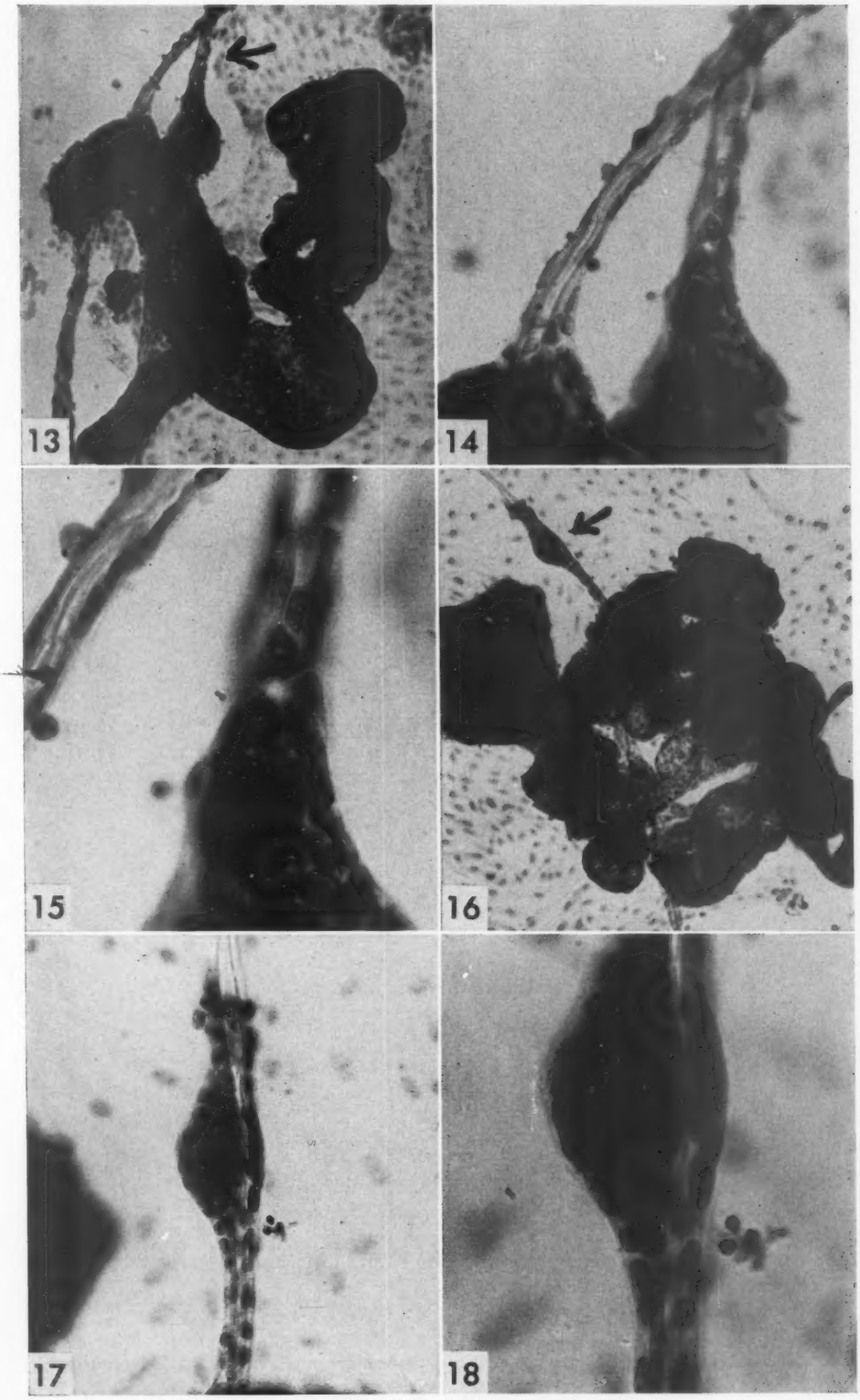
An interesting phenomenon observed during this study was the migration of endometrial cells along and around cotton fibers purposely introduced in some of the cultures. Figs. 13 to 21 illustrate this phenomenon in low, medium, and high magnifications observed in a 4 day endometrial culture from curettings of a patient operated upon on the seventeenth day of the cycle. A comparable occurrence was also noted in other fibers which, however, instead of being surrounded by cells growing out of the epithelial lining of the explant, were encircled by numerous well-differentiated histiocytes (Figs. 22 to 24).† The impression conveyed in these latter cases was that of a phagocytic action. On the other hand, the reaction illustrated in Figs. 13 to 21 appears to be of an entirely different nature and suggests an epithelialization process mirroring the way by which epithelial cells travel over the denudated surface of the endometrium to form a new epithelial lining. Such an interpretation, if correct, would provide a suitable experimental approach to the study of the mechanism of the epithelial rehabilitation of the endometrial mucosa at the end of each menstrual period or after parturition.

The tendency of cells emanating from explants to adhere to textile, glass, or other fibers introduced in tissue cultures and to follow their pathways has been previously described and is likely to represent primarily a physical phenomenon possibly of stereotropic or chemotropic attraction. Weiss,[15] in his excellent paper on "cell and axon orientation in vitro," in which he reports his observations on the migration of Schwann cells and nerve fibers along fine glass fibers, gives a detailed discussion and a very illuminating interpretation of this occurrence, defining it as a principle of "contact guidance." It is, however, evident that, aside from the basic factors underlying this phenomenon, its expression varies greatly, depending upon the intrinsic properties and potentialities of the cell types involved. This is strongly indicated by the fact that the specific pattern described by Weiss in his experiments with nerve fibers differs from the two distinct patterns observed in our cultures, one suggesting a phagocytic action and the other an epithelialization process.

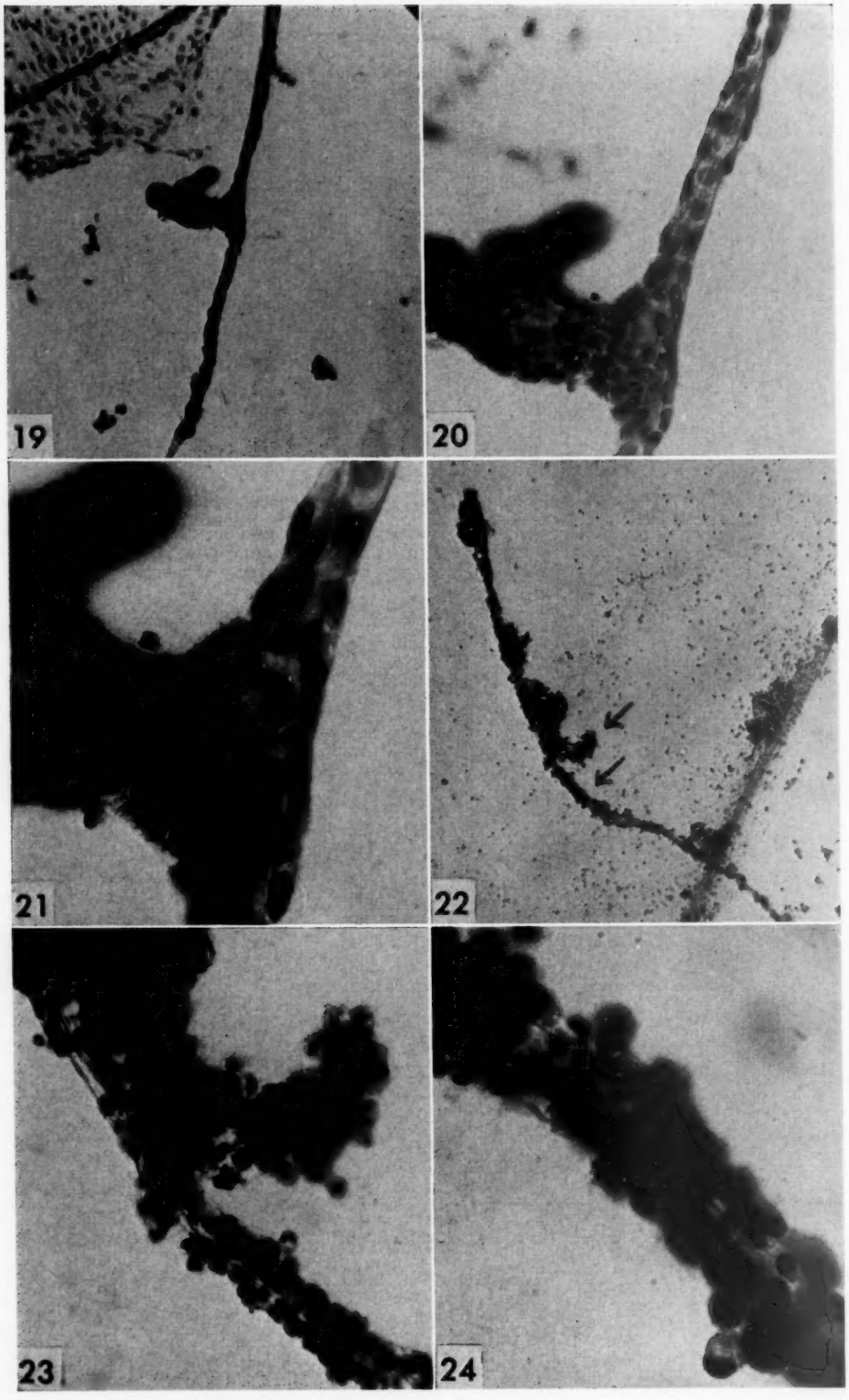
The growth activity of endometrial explants in cultures prepared from specimens taken during the menstrual stage, which was found by some investigators to be rather low or even totally absent, was fairly high in the few

*It should be noted that cultures of endometrial tissue obtained soon after curettage normally show more stromal cells and a high growth potential of both stromal and epithelial elements due to the regenerative process which generally occurs after curettage.

†A similar picture of a fiberlike structure, possibly a hair fragment, surrounded by histiocytic cells of apparently endometrial origin had previously been observed in a human vaginal smear. This was illustrated in No. 1 of Plate G IV of Papanicolaou's *Atlas of Exfoliative Cytology*,[14] and is shown here in Figs. 25 to 27.



Figs. 13-18.—Endometrial tissue culture demonstrating migration of epithelial cells around cotton fibers. (Fig. 13, ×100. Fig. 14, ×300. Fig. 15, ×600. Fig. 16, ×100. Fig. 17, ×300. Fig. 18, ×600.)

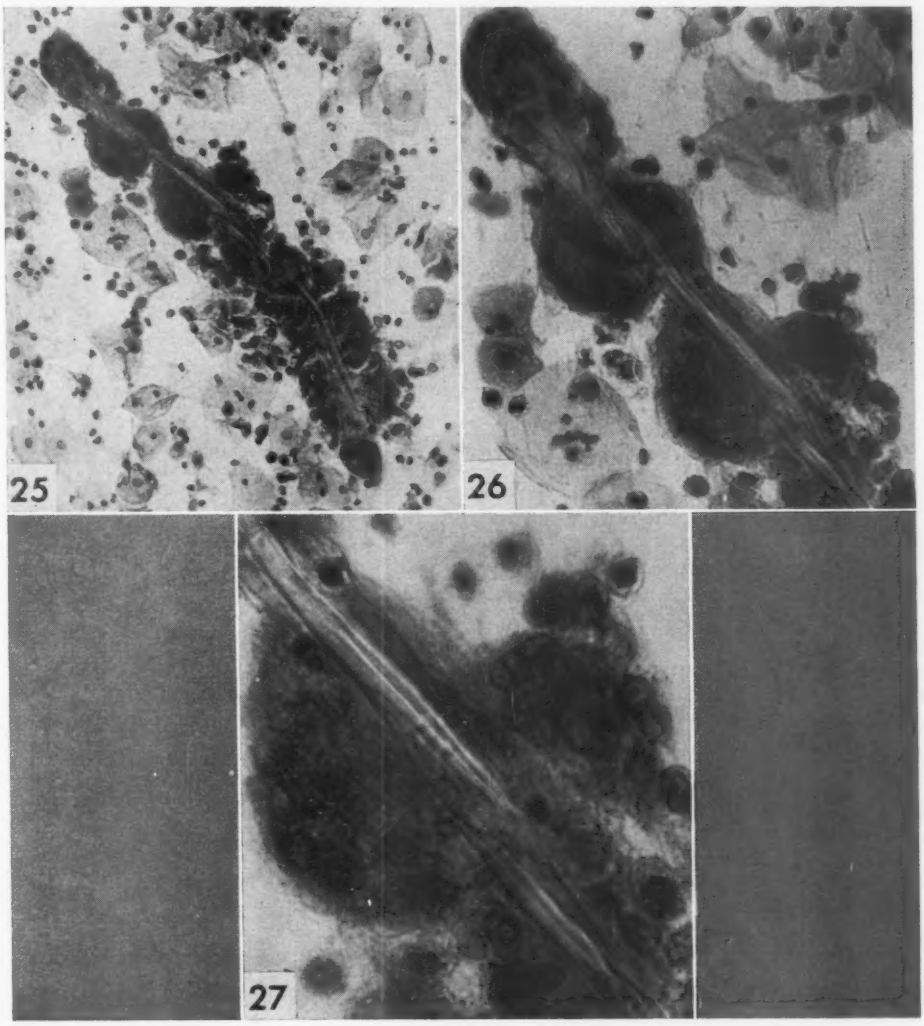


Figs. 19-21.—Endometrial tissue culture demonstrating migration of epithelial cells around cotton fibers. (Fig. 19, ×100. Fig. 20, ×300. Fig. 21, ×600.)

Figs. 22-24.—Endometrial tissue culture demonstrating swarming of phagocytic cells around cotton fibers. (Fig. 22, ×60. Fig. 23, ×300. Fig. 24, ×600.)

cases we have examined. Photomicrographs at low and high magnification from a 5 day culture are shown in Figs. 28 and 29. The specimen was taken at a hysterectomy performed on the second day of the menstrual period. A section of the surgical specimen is shown in Fig. 30.

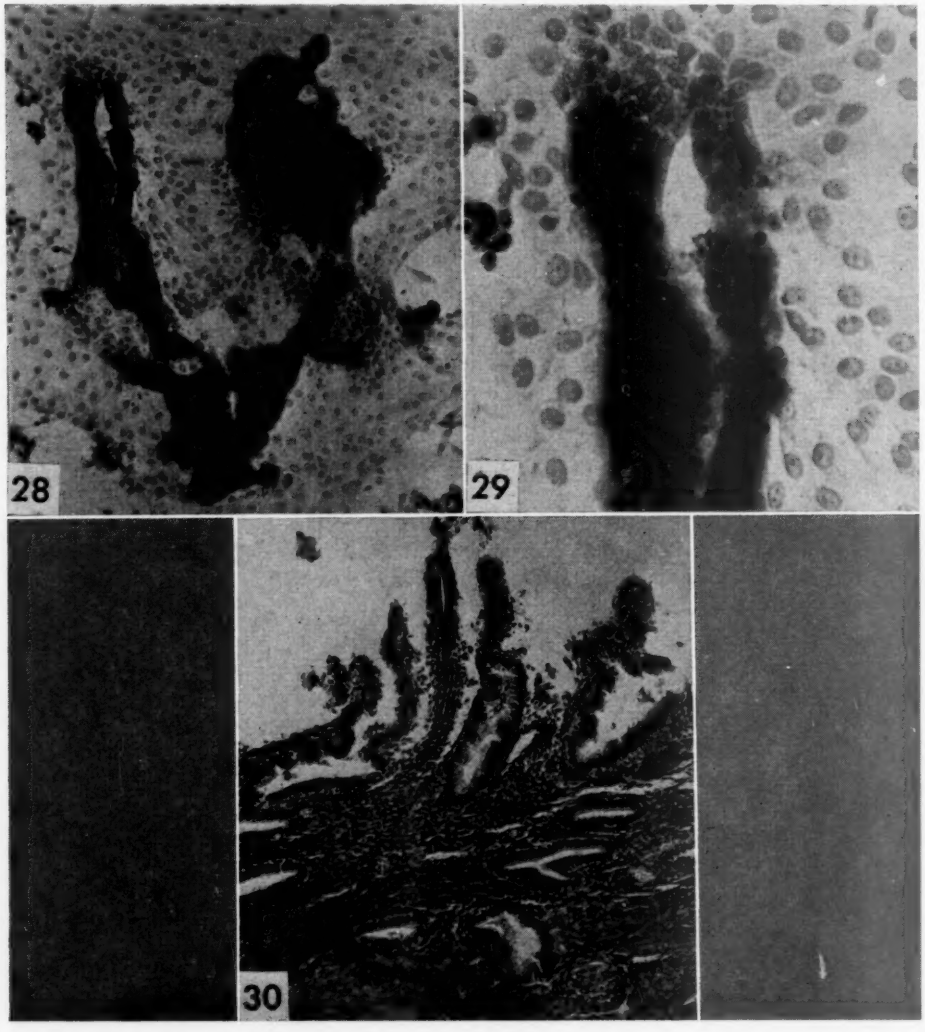
In reference to the problem of phagocytosis, which has been our starting point, the impression gathered from these studies is that some of the free cells growing out of endometrial explants are capable of phagocytic action.



Figs. 25-27.—Same phenomenon as in Figs. 22-24, observed in a vaginal smear. (Fig. 25, ×150. Fig. 26, ×300. Fig. 27, ×600.) (From Papanicolaou.[14])

This point will be discussed more fully in a separate paper. Here we will only demonstrate a few examples of it in a number of illustrations. Fig. 31 illustrates free endometrial cells phagocytosing bacteria in a tissue culture contaminated with bacilli isolated from vaginal secretion. This, as well as the next one, was taken at a higher magnification. The digestive action of the

cells upon the bacteria is shown in Fig. 32 from the same culture. An engulfment of a polymorphonuclear leukocyte is also shown in the same figure. The ingestion of Monilia in an experimentally contaminated tissue culture is illustrated in Fig. 33, while Fig. 34 shows cells phagocytosing erythrocytes which have been introduced in two different tissue cultures. No antibiotics were added to these experimental cultures.

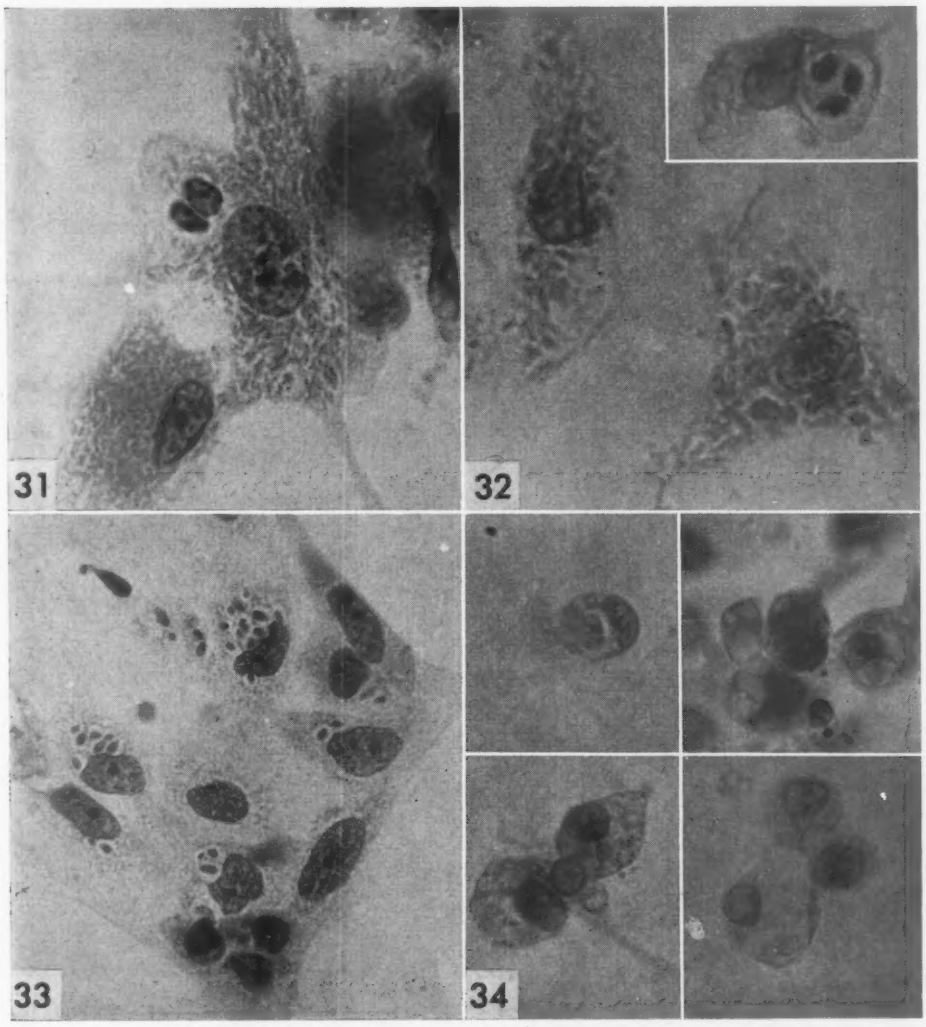


Figs. 28 and 29.—Endometrial tissue culture during menstrual phase. (Fig. 28, ×100. Fig. 29, ×300.)
Fig. 30.—Histologic section of endometrium from same case as Figs. 28 and 29. (×100.)

In many cultures the explants were surrounded by a well-defined clear area. This process apparently corresponds to that of liquefaction of the medium observed in cultures of tissues from other organs. One point of interest in our series was the observation that the bacteria or fungi in some experimentally contaminated cultures were totally disposed of and pushed back beyond the clear area, conveying the impression of a phagocytic or antibiotic action of the cells emanating from the explant. This phenomenon is

illustrated in Figs. 35 and 36. The cluster indicated by arrows is the same as the one shown at a higher magnification in Fig. 33, in which the phagocytosis of Monilia by endometrial cells derived from the explant is clearly shown.

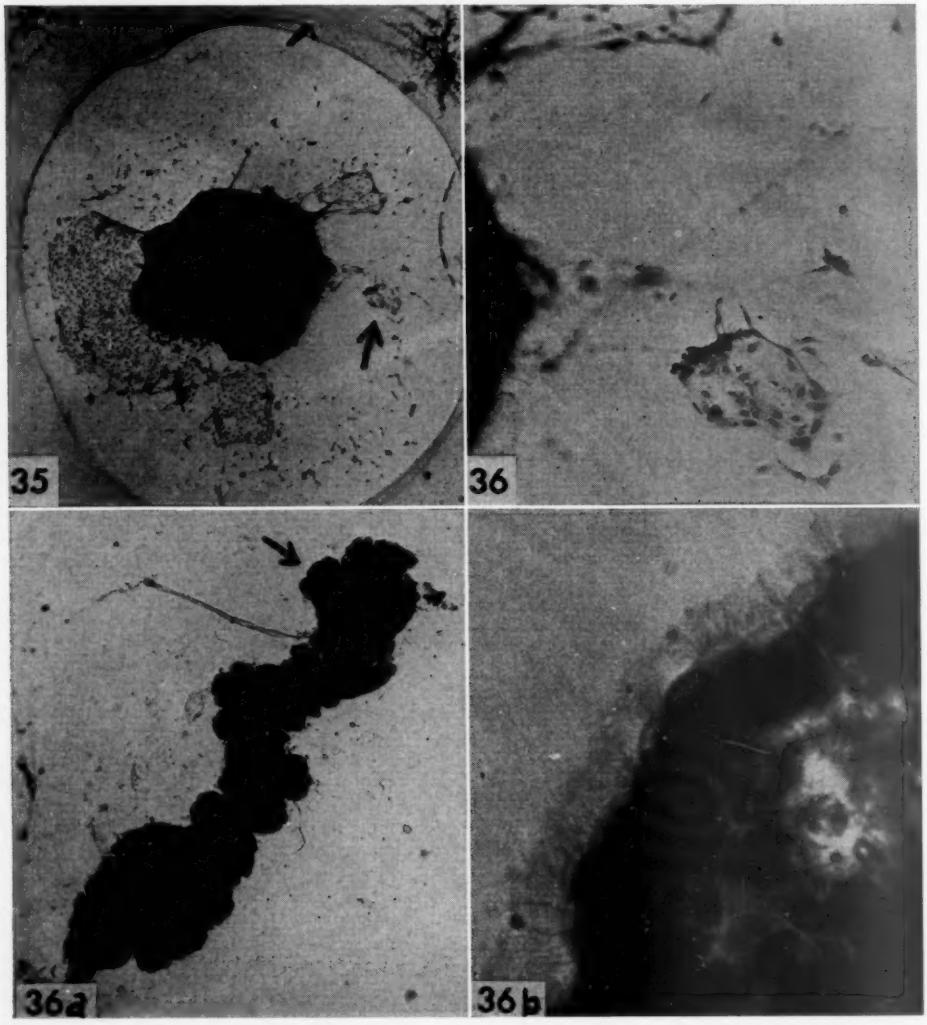
Ciliated cells were observed in a fair number of living cultures. Their ciliary movement could be distinctly seen in some instances for as long as 5 to 10 days. Many ciliated cells were detached while others formed a continuous border on the surface of the explant. In fixed and stained cultures,



Figs. 31 and 32.—Phagocytic action of endometrial cells upon bacteria. (Fig. 31, ×1,200. Fig. 32, ×1,200.)
Fig. 33.—Phagocytic action of endometrial cells upon Monilia. (×600.)
Fig. 34.—Phagocytic action of endometrial cells upon erythrocytes. (×600.)

ciliated cells were only rarely observed, probably because they were lost in the course of these procedures. It is perhaps for this same reason that ciliated cells could not always be demonstrated in sections of endometrial tissue obtained during the operation. In some instances, however, a correlation between living and fixed cultures on one hand and tissue sections on the other has been possible. In the majority of the cases in which ciliated cells were

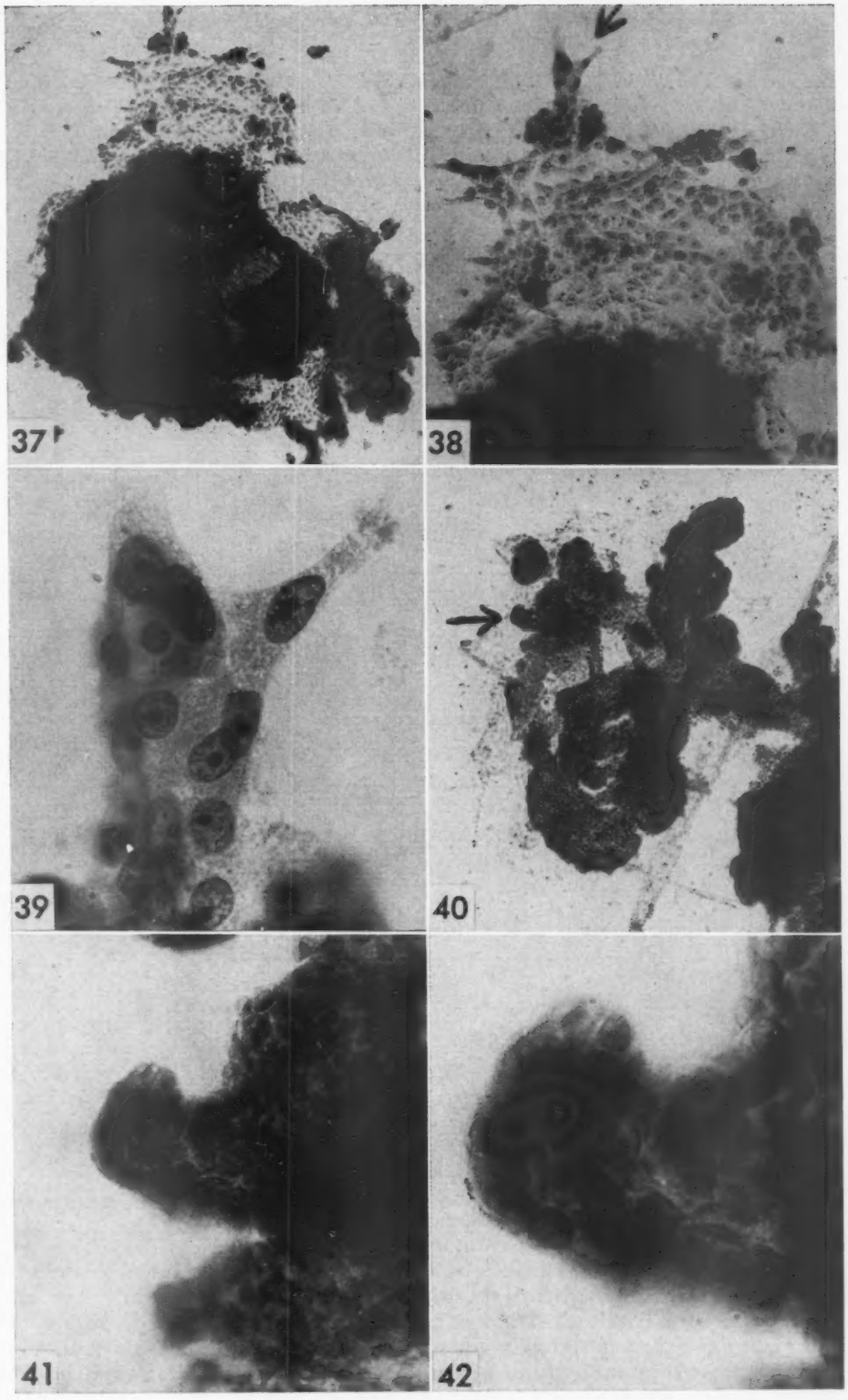
noted, the diagnosis was that of a benign endometrial polyp or polypoid hyperplasia. The best endometrial explant with a well-preserved ciliated border observed in our series in a fixed and stained 48 hour culture was in the case of an endometrial polyp (Figs. 36*a* and 36*b*). In general, explants from polypoid tissue exhibited a relatively high growth potential.



Figs. 35 and 36.—Endometrial tissue culture demonstrating clear zone around the explant. (Fig. 35, ×25. Fig. 36, ×100.)

Figs. 36*a* and 36*b*.—Endometrial polypoid fragment with ciliated border from a 48 hour tissue culture. (Fig. 36*a*, ×60. Fig. 36*b*, ×1,200.)

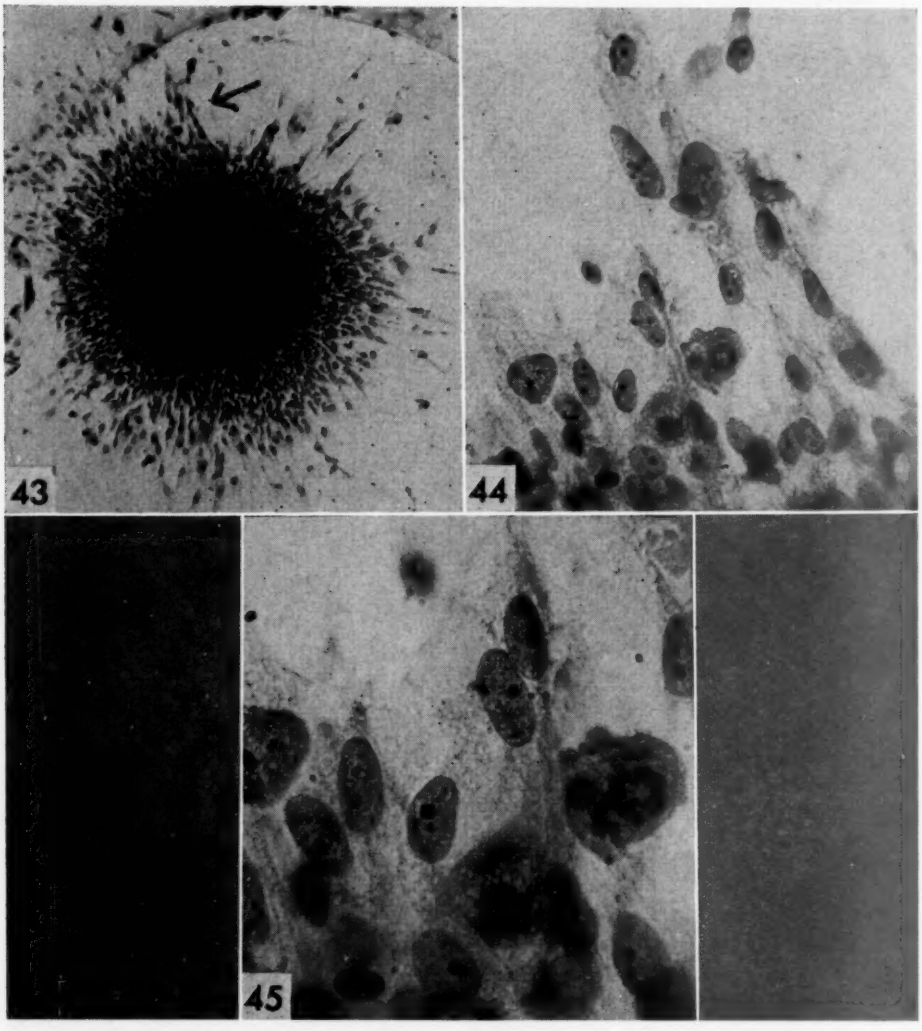
We feel that we should not conclude this presentation without demonstrating a few photomicrographs from cultures of malignant endometrial tissue. Figs. 37 to 39 illustrate the growth of an explant from an adenocarcinoma of the endometrium in a 7 day culture. Fig. 37 shows the explant and its growth at a low magnification. Fig. 38 is a higher magnification of the same explant. The area indicated with an arrow is illustrated in Fig. 39 under still higher magnification. Note the engulfment of a lymphocyte.



Figs. 37-39.—Case 1. Tissue culture of adenocarcinoma of the endometrium. (Fig. 37, ×50. Fig. 38, ×100. Fig. 39, ×600.)

Figs. 40-42.—Case 2. Tissue culture of adenocarcinoma of the endometrium. (Fig. 40, ×50. Fig. 41, ×300. Fig. 42, ×600.)

Figs. 40 to 42 illustrate an explant from a 3 day tissue culture of a papillary adenocarcinoma of the endometrium. It is rather significant that the growth pattern of this second case differs from that of the previous one, a fact which indicates that, aside from the factor or factors responsible for the malignant character of a certain cell type, there is another apparently intrinsic factor which determines the growth pattern in each individual case.



Figs. 43-45.—Tissue culture of carcinosarcoma of the uterus. (Fig. 43, ×50. Fig. 44, ×300. Fig. 45, ×600.)

The third malignant case is a carcinosarcoma of the uterus with a type of growth indicating a stromal rather than an epithelial origin. Fig. 43 of this series is from a 12 day culture of a tumor explant. The radiating type of growth resembles that previously shown in a normal case (Figs. 9 to 11) in which the growth apparently originated in the stroma. Here the cells are distinctly malignant as seen in Figs. 44 and 45 under higher magnification. Note also the mitotic figures.

The two main types of normal cells emanating from endometrial tissue culture explants and two corresponding types of cells from malignant endometrial tumors are illustrated at the same magnification in Figs. 46 to 49 for

the sake of comparison. Fig. 46 shows epithelial cells from the normal tissue culture illustrated in Figs. 5 to 8. Malignant cells of a corresponding type from the case of adenocarcinoma of the endometrium illustrated in Figs. 37 to 39 are shown in Fig. 47. Elongated cells of presumably stromal origin from a normal tissue culture (Figs. 9 to 12) and malignant cells of a corresponding type from the tissue culture of the case of carcinosarcoma of the uterus

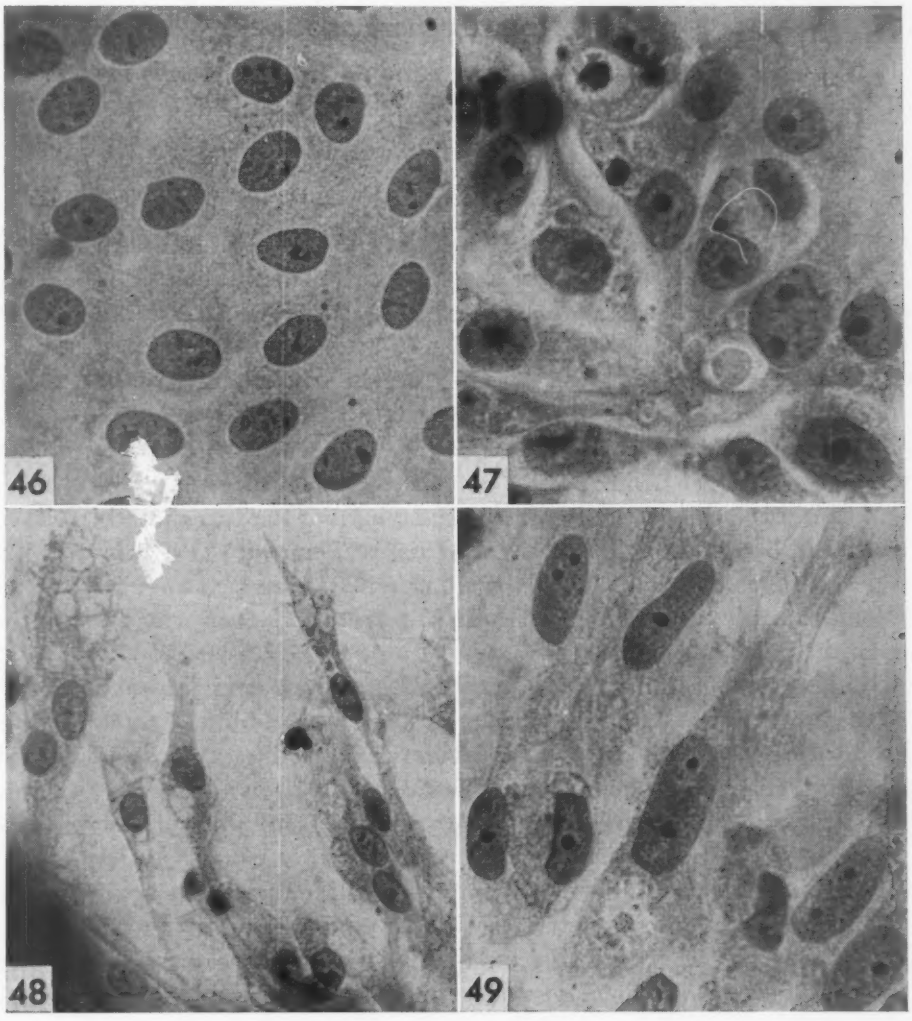


Fig. 46.—Normal epithelial cells. (×600.)
Fig. 47.—Malignant epithelial cells. (×600.)
Fig. 48.—Normal stromal cells. (×600.)
Fig. 49.—Malignant stromal cells. (×600.)

illustrated in Figs. 43 to 45 are shown in Figs. 48 and 49. The marked discrepancies in the morphologic characteristics of these four cell types are apparent. The ingestion of leukocytes and erythrocytes by the malignant cells illustrated in Fig. 47 reveals their high phagocytic activity which is not uncommon in cells originating from malignant explants.

The differences here described in the behavior pattern and the morphologic characteristics of nonmalignant and malignant tissue explants are often so pronounced as to be of real diagnostic value. In a few cases of endometrial

adenocarcinoma in which both cytologic and pathologic findings were equivocal, tissue culture proved to be extremely helpful in establishing a positive diagnosis. We thus feel that, with a technique such as the one described in this paper and the possibility of obtaining adequate culture material by the simple procedure of endometrial aspiration, this method may, in experienced hands, be a very valuable tool in the diagnosis of intrauterine malignant lesions.

Summary and Conclusions

1. Cultures of 235 specimens of human endometrial tissue, representative of all phases of the normal menstrual cycle and of various pathologic conditions of the uterine fundus, including benign and malignant neoplasms, have been studied.

2. The Maximow double cover slip method was used. Nutrient medium consisted of 1 part of a 50 per cent solution of chick embryo extract, 1 part fowl plasma, and 3 parts placental chord serum. The majority of the cultures remained in good condition for approximately 10 days or more. In one case cultures were viable until the twenty-first day. For cytologic study the cultures were preserved and stained with a modification of the Papanicolaou technique.

3. Growth activity was observed during all phases of the cycle, including the menstrual, but was found to be more pronounced during the proliferative phase. Epithelial cells growing out of the explants tend to spread in the form of sheaths of flattened cells with round or oval nuclei. It was noted that a large percentage of these are cells rushing out of the open ends of fragments of endometrial glands. Outgrowth of cells from explants was observed only in nonepithelialized areas.

4. Cells growing out of explants, consisting of stromal cells as seen during menstrual or postmenstrual stages, have an elongated form resembling that of fibroblastic or, in some instances, of endothelial elements.

5. The well-known phenomenon whereby cells growing out of explants in tissue cultures have a tendency to adhere to and follow the pathways of cotton or other fibers experimentally introduced was observed also in our cultures. It was noted, however, that two distinct patterns could be recognized, one suggesting a phagocytic action by cells of the histiocytic type, and another giving the impression of an epithelialization process by cells gliding out of the surface epithelial layer of epithelialized areas of the explant. It is thus likely that, aside from the basic factors underlying this phenomenon, its expression varies greatly, depending upon the intrinsic properties and potentialities of the cell types involved. The fact that these reactions are expressed so clearly in vitro seems to indicate that their manifestation within the body is in a way independent of any hormone or other environmental influences.

6. Evidence is presented in favor of the view that cells growing out of endometrial explants may display phagocytic action by engulfing bacteria, fungi, such as Monilia, erythrocytes, and degenerating leukocytes.

7. The process of liquefaction of the medium, which has been observed in cultures of tissues from various organs, has been a common occurrence in our

cultures. Our attention was called to a number of experimentally contaminated cultures in which the bacteria or fungi were totally disposed of and pushed back beyond the clear area, conveying the impression of a phagocytic or antibiotic action.

8. Ciliated cells were observed in a fair number of living cultures with the ciliary activity continuing for a period of 3 to 10 days. Their presence was noted chiefly in cases of polypoid hyperplasia or benign endometrial polyps.

9. Explants from malignant neoplasms of the endometrium displayed very active growth in vitro, similarly to those from benign endometrial polyps, surpassing the growth of normal endometrial tissue. Two cytologically distinct patterns could be recognized, depending upon the origin of the tumor. In adenocarcinomas and adenoacanthomas the outgrowing malignant cells were consistent with the epithelial type. In the case of a carcinosarcoma, obviously of stromal origin, the malignant cells assumed an elongated and fibrous form. These two patterns correspond to those observed in normal explants.

10. It is rather significant that in the adenocarcinoma group two distinct growth patterns could be distinguished: one in which the malignant cells grew out singly or in groups from the superficial layers of the explant; and another, characteristic of the papillary adenocarcinoma type, in which the growth of the tumor took place in the form of papillary fronds, growing out of epithelized areas. The difference in the growth pattern between these two types of adenocarcinoma seems to indicate that the malignant character of a tumor is determined by intrinsic factors which differ from those responsible for its individual growth pattern.

11. The cells growing out of malignant explants exhibited marked structural abnormalities. They tended to be larger and to assume atypical forms. Their nuclei showed considerable enlargement and notable variation in size in contrast to the nuclei of cells emanating from normal explants, which generally had a remarkably uniform pattern. Mitotic activity and phagocytic action showed a definite increase.

12. Considering that material for a tissue culture can be obtained by the simple procedure of endometrial aspiration, it is felt that, with a technique such as the one described in this paper, the examination of fixed and stained preparations of tissue culture can be very profitably used as a practical method of cancer diagnosis. What enhances greatly the diagnostic value of this method is that one deals with newly grown cells exhibiting great uniformity in size and form. The evaluation of such cells is much easier than that of the multiform cell population normally found in cytologic smears.

We wish to express our appreciation to Mr. Constantine Railey for the preparation of the photomicrographs.

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THE URINARY EXCRETION OF ANTIDIURETIC SUBSTANCES BY THE OBSTETRIC AND GYNECOLOGIC PATIENT*

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DURING the past decade there has been a growing interest in the urinary excretion of antidiuretic substances.[1-7] Extracted by a variety of techniques,[1, 7-12] substances which have an antidiuretic effect have been reported appearing in the urine of patients during the postoperative period[2, 3, 14, 15] as well as in nonsurgical conditions.[1, 4-7, 13, 16] In the present study the urinary output of such antidiuretic substances has been measured to compare the excretion rates in women, both pregnant and nonpregnant, during normal as well as pathologic and postoperative states.

Method and Material

The fundamental assay procedure is based upon the antidiuretic impact upon the rat of the material to be tested. Unfortunately, the rat responds with antidiuresis to a multiplicity of stimuli: the stress of the test procedure, the temperature of the room, nonspecific toxins in the urine, the route of injection, etc.[17-23] While a variety of assay methods have been reported in the literature, it was felt wise to establish a reliable rat assay procedure for this laboratory, which would yield consistent results in our hands. These preliminary studies occupied some six months, but furnished a test procedure which gave reproducible results.

All urine collected from patients was in the form of 12 hour specimens. The extraction method of Grollman and Woods[8] was accepted as the basis for obtaining urinary antidiuretic substances, although various modifications were considered in the preliminary comparative studies. Each collected sample was divided into four equal parts, each of which was treated in a different manner: (1) extracted by the original technique of Grollman and Woods; (2) extracted by the Grollman and Woods technique executed after the addition to the urine of varying amounts of Pitressin; (3) prepared by a modification of the same technique with the use of kaolin extraction rather than charcoal; (4) plain urine. Preliminary studies confirmed the observations of some investigators[20-24] that the intravenous route of administration yields more accurate results than does the intraperitoneal, so this route was used throughout, with the original Grollman and Woods extraction methods, applied to a 2 hour aliquot of each patient's urine.

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A colony of Holtzmann rats, from 250 to 300 grams in weight, was maintained in an air-conditioned room at 73 to 78° F. during the entire study. They were allowed food and water until the actual time of hydration. At the start of the test, each rat was subjected to gavage with 20 c.c. of distilled water and placed in a metabolism cage. One hour later gavage was repeated with another 20 c.c. of distilled water to assure adequate hydration and maximum urinary output. The amount of urine excreted was recorded every 10 minutes until a total of 10 c.c. was obtained. Gavage with distilled water was done for the third time, the number of cubic centimeters used being equivalent to the amount of urine excreted, and the test extract of the patient's urine was then injected intravenously. The extracts were divided into aliquot parts representing ½ hour, 1 hour, and 2 hour samples of urinary output. A total of at least 3 rats was used for each aliquot specimen of urine. Each group of three rats was considered a test unit, and *the average time in minutes it took to excrete 10 c.c. of urine was recorded.* Sodium and potassium determinations were done on each specimen of rat's urine and patient's urine.

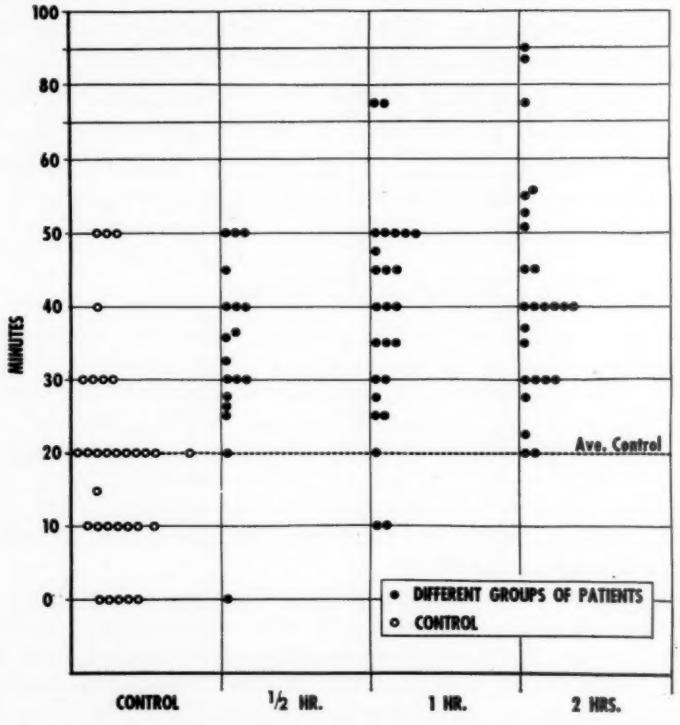

Fig. 1.—Comparative antidiuretic impact of extracts from patients' urines. Each bar represents the time in minutes required for the assay animal to excrete 10 c.c. of urine and hence the longer the bar the greater the degree of antidiuresis.

Thirty-one rats were used as controls to determine whether the injection itself caused any antidiuretic activity. The control injection was the same in volume as the extract, but distilled water was substituted for the test substance. The stress of the injection and the gavage alone produced a relative antidiuresis for 20 minutes, so the observations made during the first 20 minutes following injection of the extracts were disregarded. All figures reported represent time in excess of 20 minutes and are thought to indicate the antidiuretic activity of the patients' urine. In view of the fact that all the results

were recorded in minutes and were compared to one another and to the results obtained with the control rats, it was not felt necessary to administer ethanol to the rats in order to block endogenous production of ADH.[21, 23]

Fig. 1 depicts the contrast between the control groups, the ½ hour, 1 hour, and 2 hour urine aliquots in each particular patient grouping. The 2 hour aliquot urine extract gave the most consistent antidiuretic results and accordingly 2 hours was chosen as the unit of time for the following groups of patients. All figures reported represent the effect of extracts of a 2 hour output of urine by the patient.

Fifty-one 12 hour urine specimens were obtained by Foley catheter, extracted, and tested. The following conditions were represented (the number in parentheses indicates the number of patients in each group):

A. Obstetrics.—
1. Normal antepartum (4)
2. Normal postpartum (5)
3. Lactation (2)
4. Eclampsia, antepartum and postpartum (1)
5. Pre-eclampsia, antepartum and postpartum (2)
6. Induction with intravenous Pitocin drip (4)
7. Postpartum hemorrhage (2)
8. Cesarean section (4)

B. Gynecology.—
1. *Surgery:*
   a. Major abdominal (9)
   b. Major vaginal (2)
   c. Minor (2)
2. *General:*
   a. Premenstrual (2)
   b. Postmenstrual (2)

All patients served as their own controls and each was tested twice, once during the time interval under consideration and once either before or after that interval. The various pathologic and nonpathologic states were grouped together to determine the average for each entity.

Resulting Water Diuresis

From the point of view of diminishing the urinary output of the assay animal, the results obtained with extracts of urine from the nonpregnant patients are compared in Fig. 2. In this and the other figures, the longer the bar of the bar graph, the greater the antidiuretic activity per unit of time. Considering these results, it can be seen that there is slightly more antidiuretic substance eliminated premenstrually than there is immediately after the menstrual period. This agrees with the clinical phenomenon of premenstrual water accumulation and the corresponding postmenstrual elimination.

The pre- and postoperative studies (Fig. 2) confirm the findings of Cline[3] and Eisen[2] and their associates that antidiuretic activity is increased in extracts of the urine of patients in the postoperative period. It will also be noted, however, that the amount of this antidiuresis is proportionate to the size and impact of the operative procedure. Thus, while all patients display more antidiuretic activity postoperatively than they did preoperatively, it will be noted that this antidiuretic activity is greater following major abdominal surgery than following vaginal surgery.

This observation is of considerable interest. Such a correlation between the magnitude of the surgical procedure and the amount of antidiuretic activity has not been made previously. Since the extracts selected for testing represented a constant period of time (2 hours), this differs from the observation by Barnes[25] that the stress reaction, with its associated metabolic changes, is of the same amplitude but lasts *longer in the postoperative period* the greater the surgical procedure.

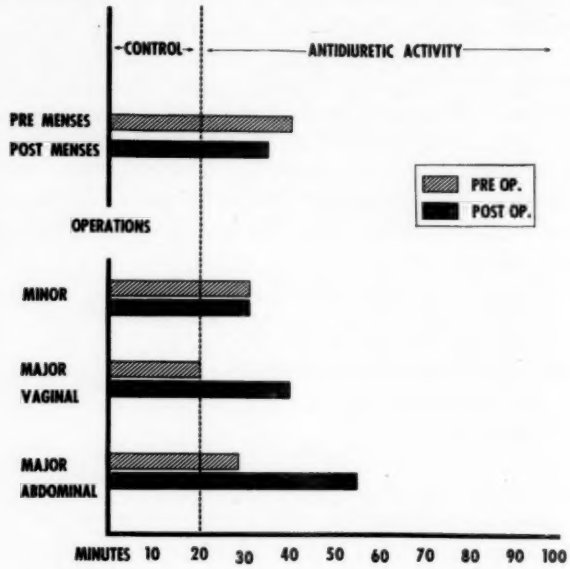

Fig. 2.—Comparison of preoperative and postoperative antidiuretic activity. There is a marked increase in antidiuretic activity in the urine of the postoperative women.

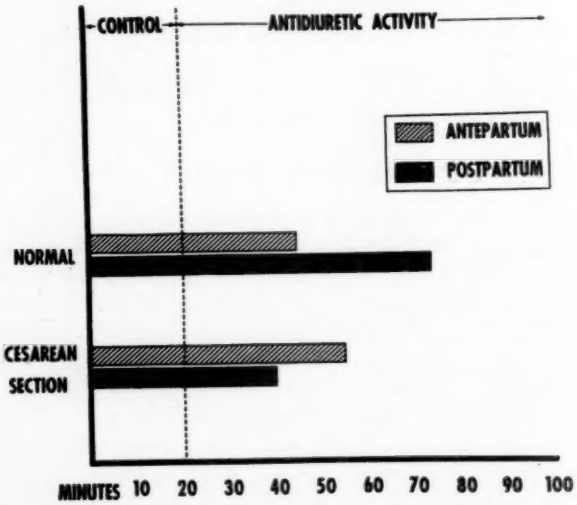

Fig. 3.—Comparative urinary output of antidiuretic substances of women following vaginal delivery and cesarean section.

The woman who has had a cesarean section has also been subjected to a surgical insult (Fig. 3). In this instance, however, the impact of the operation itself is altered by the loss of the placenta, which has been producing both

the sodium-retaining corticoids[26] and pitressinase.[27] The urinary specimens for extraction in postcesarean cases were obtained during the first 12 hours after operation before postpartum diuresis is well established. For comparison, the results following vaginal delivery are also recorded in Fig. 3, and it can be seen that they are qualitatively similar to the pre- and postoperative studies in Fig. 2, although there is quantitatively more antidiuretic activity in the urinary extract after vaginal delivery than after gynecologic surgery.

These findings in normal women ante and post partum are compared in Fig. 4 with the findings in 2 cases of pre-eclampsia and one case of eclampsia.

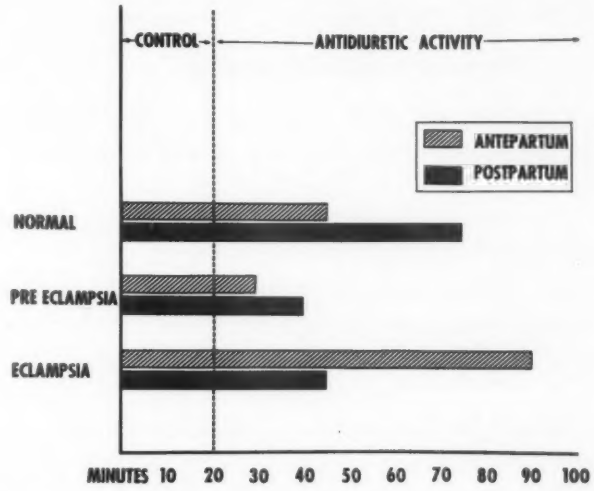

Fig. 4.—Comparative urinary output of nontoxemic women (ante partum and post partum) and women with pre-eclampsia as well as a single case of eclampsia.

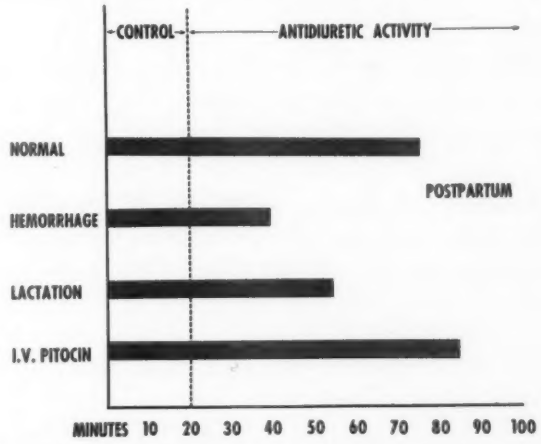

Fig. 5.—Antidiuretic activity extracted from the urine in various puerperal states.

The change in antidiuretic activity associated with pre-eclampsia corresponds to the change in normal patients except for the reduction in magnitude of the former values. These women had a relative oliguria, however, and it can be calculated that they would have exactly duplicated the pattern in the normal had a comparable urine volume been extracted. The findings in the eclamptic patient, on the other hand, duplicate those in the cesarean section patient.

In Fig. 5 the postpartum antidiuretic activity in various puerperal states is contrasted. The normal controls were nonlactating. The women who experienced a moderate postpartum hemorrhage had a relative oliguria and were producing less antidiuretic substance per unit of time than the control group. The women at the onset of lactation eliminated a greater amount; and in the face of a constant infusion of intravenous Pitocin, the greatest amount of antidiuretic activity was obtained. All of the test specimens in these women were obtained after about the same time interval post partum (except for the lactating patient, who was tested as her milk came in), although sequential studies in the other control patients during the first 2 postpartum days did not show significant changes in activity.

Summary and Conclusions

1. After a consistent method of extraction (Grollman and Woods) and assay was established, the antidiuretic activity of the urine of 41 women was tested.

2. Women with clinical premenstrual edema displayed increased antidiuretic activity in the urine during the premenstrual phase.

3. This study confirms other investigators' findings of an antidiuretic substance in the urine of postoperative patients and adds a new observation that the amount of such antidiuretic material is in proportion to the magnitude of the surgical insult.

4. The normal pregnant patient excretes a certain amount of antidiuretic material which increases (in amount eliminated per unit of time) during the first few days after delivery.

5. Following cesarean section, the antidiuretic effect of the operation itself is apparently masked by this postpartum shift toward diuresis seen in the vaginally delivered patient.

6. The eclamptic patient displays an overwhelming amount of antidiuretic activity, which may be a factor in the phenomenon of fluid retention and oliguria. This antidiuretic activity decreases once delivery has been accomplished.

7. Under the conditions of this study, lactation was associated with a decreased amount of antidiuretic activity in the urine (tested when lactation was initiated) compared to that of the nonlactating postpartum patient (tested the first postpartum day).

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A NEW CLINICAL TEST FOR THE EFFICACY OF PROGESTERONE COMPOUNDS*

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IN 1898 Louis Auguste Prenant suggested that the corpus luteum was a gland of internal secretion and 2 years later Gustav Born hypothecated that the function of the corpus luteum was concerned with the protection of the early embryo. Great advances were made to elucidate the function of the corpus luteum by Ludwig Fraenkel, by Ancel and Bouin, by Leo Loeb and others, which led to isolation of the principal hormone of the corpus luteum, i.e., progesterone, by Allen and Corner, Fels and Slotta, and Fevold and Hisaw. Finally, in 1934, Butenandt succeeded in synthesizing progesterone.[1]

Many tests for progestational activity have been described, all of them based on the discovery by Ancel and Bouin that the secretory changes of the endometrium were caused by the corpus luteum. Briefly, the Corner-Allen test for progesterone activity is to mate a rabbit, remove the ovaries next day, and then administer the "test substance" to see whether it will cause progestational proliferation and, if so, how much is required. This test as well as the modifications offered by Clauberg and by McGinty are tests of progesterone activity. The ultimate purpose of progesterone (with the proper admixture of estrogens), however, is to maintain pregnancy. Actually the experiments first performed by Fraenkel, wherein he surgically destroyed the corpora lutea of rabbits which had mated 6 days before with no pregnancy ensuing, set the real basis for the test of progesterone efficacy. The maintenance of pregnancy by the "test substance" after removal of the corpus luteum in the experimental animal has become the recognized test for progesterone efficacy. Unfortunately, laboratory testing cannot always be equated with human requirements.

Many new steroids with progestational activity have become available for clinical use. These substances have been shown to have progestational activity not only in test animals but also in humans by certain clinical criteria. These

*Acknowledgment is made for the following progestational agents used in this study:

Norlutin, 17-alpha-ethinyl-19-nortestosterone (Parke, Davis & Company, Detroit, Mich.: also Syntex Laboratories, Mexico City, Mexico).

Enovid, norethynodrel with ethinyl estradiol 3-methyl ether (G. D. Searle & Co., Chicago, Ill.).

Colprosterone, progesterone vaginal suppositories (Ayerst Laboratories, New York, N. Y.).

Prodox, 17-acetoxyprogesterone (The Upjohn Company, Kalamazoo, Mich.).

Delalutin, 17-alpha-hydroxyprogesterone caproate (E. R. Squibb & Sons, New York, N. Y.).

Nilevar, 17-alpha-ethyl-17-hydroxy-norandrostenone (G. D. Searle & Co., Chicago, Ill.).

Pranone, 17-ethinyl testosterone ethisterone (Schering Corporation, Bloomfield, N. J.).

Lutocylol, 17-ethinyl testosterone ethisterone (Ciba, Summitt, N. J.).

Braxorone, 9-alpha-bromo-11-ketoprogesterone (E. R. Squibb & Sons, New York, N. Y.).

criteria are: (A) the induction of withdrawal bleeding in castrate women primed with estrogens or in amenorrheic women with adequate endogenous production of estrogens, (B) thermogenic effect, (C) secretory changes in the estrogen-primed endometrium, and (D) inhibition of ferning of the cervical mucus.[2]

Many progestational agents meet the criteria of progestational activity. But activity and effectiveness are not synonymous and are not readily equated.

Smith and Engle, Hisaw, and Corner have shown that progesterone can prevent estrogen withdrawal bleeding. Progesterone withdrawal is the important hormone in uterine bleeding for it has been shown by Corner, Zuckerman, Hisaw, and Greep, that the castrate monkey maintained on estrogens will bleed after discontinuance of a course of progesterone in spite of continued and even more intensive estrogen therapy.[1] Furthermore, it has long been known that, in the human, upon removal of the ripening corpus luteum, a menstrual period will follow within 48 to 72 hours. In the light of these known facts the following simple test for efficacy of progestational compounds is proposed.

An index of the efficacy of any progestational compound in the human female may be ascertained by determining the amount of the testing substance required to delay the onset of menses in normal ovulating women. The agent is administered daily from day 20 or 21 of the cycle (or 6 or 7 days after the occurrence of ovulation as determined by the basal temperature record) for a period of 3 weeks or longer. The ability of the progestational compound to continue to support the endometrium in spite of the normally regressing corpus luteum indicates that the substitutional agent has progestational activity equal to or greater than that of the normal corpus luteum.

Progesterone parenterally in doses of 75 to 100 mg. (which evokes a painful local reaction in most instances) is capable of postponing menses for 1 to 3 weeks. However, when ethisterone (17-ethinyl testosterone) was put to the test, 300 mg. per day failed to prevent the onset of the ensuing menses, while 400 to 500 mg. per day proved successful. Twelve hundred milligrams of 17-acetoxyprogesterone per day proved unsuccessful; so too did a daily oral dose of 1,500 mg. of 17-hydroxyprogesterone caproate. Progesterone suppositories in doses of 250 mg. per day failed, and at 500 mg. dose levels menses could be postponed only one week. The addition of small amounts of an estrogen (0.1-0.2 mg. stilbestrol per day) did not enhance the effectiveness of the compounds.

The only agent that successfully postponed uterine bleeding was a member of the new 19-nortestosterone derivatives, i.e., 17-alpha-ethinyl-19-nortestosterone (Norlutin). Twenty to thirty milligrams of 17-alpha-ethinyl-19-nortestosterone administered daily from the twentieth or the twenty-first day of the cycle consistently postponed the onset of menses for the duration of medication (3 weeks to 6 months). In only 3 of the 70 trials did break-through bleeding occur, and in 2 this took place only after 2 or 3 months of continuous medication; no delay was effected in the third.

Similar studies are being performed with the use of such oral progestational compounds as 17-alpha-ethyl-17-hydroxy-norandrostenone (Nilevar), norethynodrel with the addition of ethinyl estradiol 3-methyl ether (Enovid), and 9-alpha-bromo-11-ketoprogesterone (Braxorone). A preliminary impression has been gained that these progestogens may be effective in meeting the test in doses varying from 30 to 60 mg. per day.

Conclusion

The ability of agents with known progestational activity to postpone menses in normal ovulating women may be used as an index of efficacy, if the agent to be administered is started 6 or 7 days after ovulation and continued for 3 weeks or longer. On the basis of this particular test it appears that 17-alpha-ethinyl-19-nortestosterone is 15 to 20 times as effective as 17-ethinyl testosterone (ethisterone) and 4 to 5 times as effective as parenteral progesterone.

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PELVIC LYMPH NODE DISSECTION FOLLOWING RADIOTHERAPY

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THE problem of the lymph node has frequently been considered a crucial factor in the treatment of cervix cancer. Of the three principal areas of interest for treatment—the primary lesion, the parametrium, and the nodes—it has been postulated that either modality, radium or surgery, could control disease in the first two, but that surgery alone offered the possibility of cure in cases with node involvement.[1] It was natural for gynecologists to remove the pelvic nodes at the time of radical hysterectomy because only such a procedure satisfied the requirements of cancer operations elsewhere in the body. Indeed, the renaissance of radical hysterectomy in the past decade was partly conditioned by the belief that radiation was defeated not only by radiation-resistant tumors, but also by any cancer already established in lymph nodes.

In 1934 Leveuf[2] and Taussig[3] independently suggested that the solution to the problem of this supposedly radioresistant tumor in the pelvic nodes might be a pelvic lymphadenectomy after completion of radiotherapy. Leveuf reported only 3 such cases, but in 1943 Taussig[4] reported 175 transperitoneal node dissections with 26.8 per cent incidence of positive nodes. Twenty-one per cent of the patients with positive nodes survived 5 years and he credited this procedure with a 10 to 15 per cent improvement in his results. Following Taussig's lead, Morton[5] operated on 103 patients by the transperitoneal route. He noted that the incidence of positive nodes was reduced from 30 to 16 per cent in the patients who had completed radiotherapy before operation. He had only 2 long-term survivors among the patients with positive nodes, however, and suggested that the place of the pelvic node dissection as therapy remained to be established.

Nathanson[9] proposed the extraperitoneal approach to the pelvic nodes, emphasizing the ease of access to this area by this technique, especially in the obese patient. Meigs, Parsons, and Nathanson[6] reported an incidence of 28 per cent positive nodes in 75 patients operated upon by this route, but noted that the incidence was less in patients who had been treated with supervoltage therapy. The largest series of extraperitoneal lymph node dissections reported is that of Gorton[7] in 1957 with 364 patients from Lund, Sweden. He noted

a diminution in the incidence of positive nodes following radiation from 30.0 to 13.6 per cent, and was convinced that the survival rate in Stage I and II carcinoma of the cervix was improved 15 per cent by the addition of this operation to routine therapy. A preliminary report on a small series of extraperitoneal lymphadenectomies has appeared from the M.D. Anderson Hospital by Wall and Arnold.[8]

Material

In 1952 it was decided that all patients with Stage I and Stage II carcinoma of the cervix who were to receive standard radiation treatment at the Sloane Hospital for Women and the Francis Delafield Hospital would have an extraperitoneal node dissection as described by Nathanson[9] three months after the completion of radiotherapy if the primary lesion proved healed. At a later stage of our experience the transperitoneal route was occasionally used. These patients usually received 6,000 mg. hr. of radium in 100 hours with the Corscaden applicator; this application gives approximately 8,000 to 10,000 gamma to point A. The external radiotherapy varied, but in general consisted of either 3,500 r tumor dose given by a 250 kv. machine, or 5,000 r given by the supravoltage units: the 24 Mev betatron, the 2 Mev machine, or the cobalt^{60} unit. Sixty per cent of the patients were treated by one of the supervoltage techniques.

Of the 72 patients who composed the primary radiotherapy group from 1952 through 1956, 55 were subjected to pelvic lymphadenectomy. Forty-three patients were operated on by the extraperitoneal route and 12 transperitoneally. These cases were distributed according to the International Classification as follows:

Stage I	28
Stage II	23
Stage III	4

Five patients refused operation and another 6 were rejected on medical grounds. There were 6 patients in whom persistent or recurrent primary disease was found at the time of the preoperative biopsy.

Results

The incidence of positive nodes in the various stages of advancement is given in Table I and can be compared with the corresponding figures for radical hysterectomy and node dissection at this hospital in Table II. Of the 51 patients with Stage I or Stage II lesions on whom pelvic node dissections were performed, only one was found to have positive nodes after full radiotherapy, an incidence of 2 per cent, whereas the incidence of positive nodes was 18.5 per cent in the patients on whom radical hysterectomy was performed as the primary method of treatment.[10] Six patients were rejected for general medical reasons, although 7 of the patients on whom operations were performed were over 60 years of age and many had moderate hypertension. All series of cases will have some selection on such grounds. The condition of the nodes in the 6 patients with persistent primary disease at cervical biopsy 3 months after the completion of treatment is known in all cases as the result of radical hysterectomy and node dissection, exploratory operation, or autopsy. An autopsy was also performed on one patient who died of heart disease, making a total of 58 patients with Stage I and Stage II lesions in whom the pelvic nodes were examined following radiotherapy. There were 3 patients

with positive nodes in this more inclusive group containing the radiation-resistant patients, an incidence of 5.2 per cent. It is of interest to note that 3 patients in whom radical hysterectomy was performed for persistent cervical disease had negative pelvic nodes.

TABLE I. DISTRIBUTION OF POSITIVE NODES

	NO. OF CASES	NO. OF POSITIVE NODES
Stage I	28	0
Stage II	23	1
Stage III	4	2

TABLE II. LYMPH NODE RESULTS AFTER RADICAL HYSTERECTOMY

	NO. OF CASES	NO. OF POSITIVE NODES
Stage I	44	5
Stage II	17	6
Total	61	11 (18.0%)

Complications

Of the 55 patients who had lymphadenectomies, 14 had a completely uneventful postoperative course and an additional 21 had only minor complications. There were 20 patients whose complications involved major disabilities or long periods of hospitalization. The single death was caused by a pulmonary embolus 6 weeks after operation.

If the complications are divided into those which occurred in the immediate postoperative period and those that were delayed, it is found that 7 had immediate complications, 10 had both immediate and delayed complications, and 24 had only delayed complications. There seemed to be little relationship between the immediate and delayed complications (Table III).

TABLE III. COMPLICATIONS

Immediate.—	
Wound infection	13
Urinary tract infection	4
Atelectasis	2
Thrombophlebitis	1
Paralytic ileus	1
Delayed.—	
Leg edema	25
Wound complications	9
Lymphocysts	9
Thrombophlebitis	7
Bowel complications	3
Hydronephrosis	3
Vesicocutaneous fistula	1
Homologous serum jaundice	1
Pulmonary embolus	1

The category which is unusually large is that of wound infection, the 25 per cent incidence of which can be compared to 0.85 per cent for the gynecologic service as a whole.

Thirty-four complications occurred after discharge of the patient from the hospital; 15 of these were severe enough to require readmission. Our most common complication, leg edema, was also the most common complication reported by Gorton. In these 25 patients, the edema was minimal in 13 and

probably due to recurrent disease in 4, leaving 8 patients with moderately severe edema apparently caused by the operation. The late wound complications consisted, for the most part, of the drainage of clear fluid through the incisions for periods up to 18 months.

The development of lymphocysts has been reported in the Japanese literature as a complication of the Okabayashi operation by Kobayashi[11] and Mori.[12] Our experiences with this entity have been previously reported in detail.[13] The lymphocyst is a collection of serous fluid which develops retroperitoneally in the region of the iliac vessels. In 8 of our 9 patients this condition was diagnosed clinically, the other at autopsy. The cause of death in the patient with the pulmonary embolus was considered by the pathologists to be thrombosis of the pelvic veins secondary to displacement of these veins by massive bilateral lymphocysts. Six of our patients with lymphocysts required secondary operations because of the cysts and the patients whose cysts became infected required prolonged hospitalization.

Pelvic thrombophlebitis might be expected in an operation in which the great vessels of the pelvis are dissected and displaced. One of our 8 cases appeared in the immediate postoperative period and the other 7 were delayed for periods up to one year. Nathanson reported 2 deaths due to pulmonary emboli in his series of 75 patients, an incidence comparable to our own. Prophylactic anticoagulation therapy was not effective in preventing the development of thrombophlebitis.

The complications of the urinary tract and bowel which necessitated bilateral nephrostomies in one patient and left one patient with a vesicocutaneous fistula, 2 with colostomies, and one with stenosis of the rectosigmoid are such that it is impossible to separate radiation damage from surgical injury, but it seems probable that poor healing of the heavily irradiated tissue contributed to the surgical morbidity.

Of the total of 55 patients, 20 are now living and well; 13 have died of their original disease, including all of those with positive nodes. Sixteen patients continue to have symptoms secondary to the pelvic lymphadenectomy or to the combination of radiotherapy and lymphadenectomy. There are 5 with symptoms due to radiation injuries. The most common persisting symptom has been edema, still noteworthy in 10 patients.

Comment

Whether one considers the 2 per cent incidence of positive nodes in the patients who actually came to node dissection according to plan or whether one considers the somewhat greater incidence of 5.2 per cent in all patients in whom pathologic examination on pelvic nodes was possible, including those with grossly radioresistant primary disease, the incidence of positive nodes in this series is the lowest yet reported. The majority of Taussig's patients had Stage II carcinomas of the cervix operated upon 2 weeks after the completion of radiotherapy. He found an incidence of 26.8 per cent positive nodes. Morton found 30.0 per cent positive nodes in patients who had not received preoperative external therapy and only 16.3 per cent in those who had. Similarly, Meigs and Nathanson reported 28 per cent positive nodes, but only 12 per cent in patients treated with a 1,200 kv. machine. Gorton reported 16 per cent positive nodes after radiotherapy but the dose of external radiation given these patients was low.

For many years it was believed that radiotherapy was ineffectual in the treatment of metastatic tumor in lymph nodes. This impression was formed in the years when external radiation delivered a far less than cancerocidal dose to the side wall of the pelvis. Our studies support the viewpoint that modern high voltage radiotherapy can effectively attack these nodes. It will be noted that the tumor dose given to the patients in our series was in all cases maximal for the mode of therapy used, whether by 250 kv. machine or by the supervoltage techniques. With these larger amounts of radiation the incidence of radiation injuries may be expected to be higher than usually encountered.

The complications seemed more numerous than those seen after radical hysterectomy on our service; the failure of healing of heavily irradiated tissue possibly accounted for this high incidence. The complications which resulted in nephrostomies and colostomies in a few patients suggest a combination of radiation and surgical trauma. Although Mori[12] related the formation of lymphocysts primarily to the amount of tissue removed, he found that the incidence of lymphocysts was higher in a small series of patients who received preliminary radiotherapy than in the group as a whole.

The morbidity and mortality following pelvic node dissection after full radiotherapy provide a strong argument against this regime as a routine therapeutic measure, as does the paucity of positive nodes, and the death of the patients with positive nodes despite node dissection.

Summary and Conclusions

1. Pelvic lymph node dissection after full radiation treatment for cancer of the cervix carries a prohibitive morbidity and is not therapeutically sound.

2. Modern radiation therapy appears to have the capacity to destroy metastatic cervical cancer in pelvic lymph nodes, leaving a residue too small to warrant an adjuvant surgical approach to them.

3. The combination of radical radiation treatment and radical surgical treatment is very traumatic.

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THE MANCHESTER-FOTHERGILL OPERATION, ITS PLACE IN GYNECOLOGY

A Review of 960 Cases at University Hospitals, Iowa City, Iowa

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WITHIN the last 10 years vaginal hysterectomy with plastic repair has become the favorite method of treating uterovaginal prolapse in many clinics.[1, 2, 3] It is the purpose of this paper to present our experience with the Manchester-Fothergill operation, and to review our concepts of this procedure. There are many who feel it has little place in the treatment of uterovaginal prolapse and that it should be discarded. In this clinic, it is felt there are three procedures, the LeFort operation, vaginal hysterectomy with repair, and the Fothergill operation, of value in the treatment of prolapse. Each has a definite place in the management of certain relaxations. The long-term use of a pessary in the treatment of prolapse is undesirable except in those rare instances where the physical condition of the patient precludes any type of surgery. In patients with significant vaginal relaxation, operative correction gives the best results.[3, 4, 5]

The primary features of the Manchester-Fothergill operation are the plication of the fascia of the anterior vaginal wall, amputation of the cervix, shortening of the cardinal ligaments, and a high posterior vaginal wall repair. A dilatation and curettage is done preceding the operation to detect unsuspected uterine disease and to facilitate approximation of the vaginal mucosa to the amputated cervix.

Donald, of Manchester, England, in 1888, was the first to combine the components of this operation for the treatment of genital prolapse. It is true that parts of the operation had been used separately before Donald combined them into a single procedure. The popularity and the usefulness of this operative procedure were spread by Fothergill, a voluble student of Donald. Consequently, the operation is often called the Fothergill, or the Donald-Fothergill. Since Manchester, England, was the location of the women's clinic where these men worked as gynecologists, the name of this city has been advocated as a name for the operation.

Over the years there have been many minor modifications of the basic principles of the Manchester procedure. Fothergill[6] modified Donald's original

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operation merely by changing the direction of the incision line in the anterior wall of the vagina. The minor differences in the technique of various surgeons are of little consequence when compared to the principle that the operation utilizes an extraperitoneal exposure which is easier, shorter, and safer to the patient than such operations as the vaginal hysterectomy with repair.

Material

At the State University of Iowa Hospitals from 1936 to 1955, there have been 960 patients treated by the Manchester-Fothergill procedure for genital prolapse. The chart of each patient was carefully reviewed and pertinent information was recorded on punch cards for analysis. Fig. 1 shows the number of vaginal hysterectomies and Fothergill operations done each year. There has been a gradual increase in the number of vaginal hysterectomies performed during the last few years. This has been chiefly due to a desire to familiarize residents with the technique of this procedure and to a lesser extent to the broadening of indications for vaginal hysterectomy.

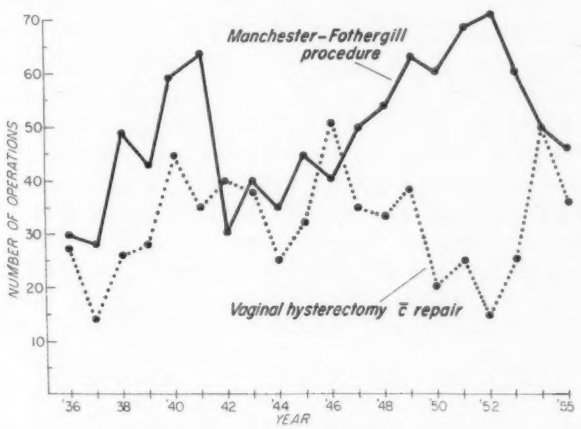

Fig. 1.—The incidence of the Fothergill operation compared to that of vaginal hysterectomy.

The symptomatology of the patients operated upon for prolapse was carefully evaluated from the clinical record. Such symptoms as headache, lower abdominal pain, and constipation were infrequently recorded. A few patients had such urinary symptoms as frequency and burning, suggestive of chronic cystitis due to urinary retention. Careful determinations of residual urine in a large number of patients with varying degrees of prolapse have rarely been found to be significant, however. Often the patients with a large prolapse have very few symptoms, while those with minimal relaxation may have a long list of unrelated complaints. The most constant significant symptom was the presence of a bulging mass at the introitus or the sensation of something falling out, which was present in 82 per cent of the cases (Table I). Urinary hesitancy or difficulty in starting the urinary stream occurred in 15.8 per cent of the patients. Stress incontinence was a significant symptom in 150 patients, or 15.6 per cent. Urge incontinence or the inability of a patient to hold back urination when she has the desire is probably unrelated to vaginal relaxation, but is due to a nerve imbalance involving the bladder and is occasionally encountered in the aging patient coincidentally with vaginal relaxation. This is a symptom complex that is most difficult to treat and often is not cured by a vaginal plastic and often is made worse.

At the time of pelvic examination the majority of patients had the anatomic triad of cystocele (89 per cent), rectocele (79 per cent), and some degree of uterine prolapse (72 per cent). There were some patients with severe prolapse with ulcerations of the cervix or vaginal walls. There were the usual findings of cervical disease such as chronic cervicitis, laceration, eversion, erosion, and Nabothian cysts. There were 2 patients, not included in this operative series, with a complete prolapse who had extensive epidermoid carcinoma of the cervix and were treated by x-ray and radium.

TABLE I. SYMPTOMATOLOGY OF UTEROVAGINAL PROLAPSE

SYMPTOM	NO. OF PATIENTS	%
Feeling of a mass	791	82.3
Urinary hesitancy	152	15.8
Stress incontinence	150	15.6
Urge incontinence	10	1.0
Fecal incontinence	9	0.9
No symptoms	94	9.7

Selection of Patients

Vaginal hysterectomy was elected in the patient with (1) relaxation associated with abnormal bleeding or uterine disease, (2) complete prolapse, (3) an incomplete prolapse where the uterus was small and came down well, and (4) the desire to have uterus removed in conjunction with the repair. The patient should be in reasonably good health and a good surgical risk. The procedure was avoided on the very elderly patient. The Fothergill procedure was advised in (a) the patient with a long, hypertrophied cervix, (b) the patient who has had previous pelvic surgery, (c) the patient who does not desire removal of the uterus, (d) the elderly woman who desires that the functional capacity of the vagina be maintained, and (e) the poor-risk patient.

It is felt that in many cases either a vaginal hysterectomy with repair or a Fothergill procedure will give equally good results in the management of uterovaginal prolapse. Prior to operation we discuss with the patient and her husband what anatomic defects are present, the type of operation we propose doing, and the symptoms we think can be benefited. If the husband and/or wife do not desire hysterectomy, this wish will be honored.

In the past the Fothergill operation combined with vaginal tubal ligation was selected for certain patients in the childbearing age who had severe relaxations and prolapse which required surgical correction. At present, if a patient in the childbearing age needs operation, no doubt vaginal hysterectomy would be selected unless future pregnancies were desired. We have always advised patients who wish children after a successful Fothergill operation that they should be delivered by cesarean section to protect the repair. Many of the earlier reports[7, 8] did not express the opinion that vaginal delivery offers any difficulty or leads to future relaxations. The effect of amputation of the cervix on premature labor was not mentioned.

Results

Surgical Complications.—The Fothergill operation usually required between 90 and 120 minutes and was performed under gas anesthesia. There were no deaths recorded during operation. Major surgical complications, such as bowel or bladder injury, were infrequently encountered even though the majority of the operations were performed by residents. In 3 instances the bladder was

inadvertently opened but immediate closure of the defect prevented subsequent complications. In 2 cases the rectum was entered during a repair of the posterior vaginal wall. Both defects were immediately repaired, one successfully; the other, however, became infected and resulted in a rectovaginal fistula which required subsequent repair. To our knowledge no ureteral damage was recognized but in one patient a urethrovaginal fistula developed on the seventh postoperative day.

One of the disadvantages of the Fothergill operation that has been frequently mentioned is that it does not offer protection against future uterine malignancy. This has not been our experience. In this series amputation of the cervix seemed to give complete protection against future cervical malignancy, as no cases of squamous-cell carcinoma occurred in the follow-up group. Two patients in this series, however, had early invasive epidermoid carcinoma, diagnosed from the microscopic examination of the amputated cervix. One other patient was readmitted 5 months after a Manchester operation with an adenocarcinoma involving the amputated stump. This was present at the time of operation and had been histologically misinterpreted as endocervical glandular hyperplasia. These 3 patients were treated with conventional deep x-ray and radium, and all were alive and well with no complications 5 or more years after therapy. To our knowledge no proved cases of malignancy of the fundus have occurred on follow-up examination. Our experience, therefore, definitely indicates that leaving the body of the uterus and the inner part of the cervix constitutes no hazard to the individual from the development of endometrial or cervical malignancy.

In determination of the average blood loss from the Manchester procedure, the obvious inaccuracies in estimating blood loss must be considered. Only 20 per cent of the patients required transfusions, either single or multiple, during or following operation. There may be some discrepancy in this as a measure of significant blood loss since transfusion was hesitatingly used until the mid-forties in our hospital. This incidence of required transfusions should be considered with the knowledge that most of the plastics were done by the resident staff.

TABLE II. CAUSES OF POSTOPERATIVE FEVER IN 605 PATIENTS

CAUSE	NO. OF PATIENTS	INCIDENCE (%)
Infected operative bed	524	84.7
Urinary tract infection	64	10.3
Respiratory infection	6	1.0
Pelvic cellulitis	7	1.1
Thrombophlebitis	8	1.3
Infected perineal repair	7	1.1
Broad ligament abscess	1	0.2
Pelvic peritonitis	1	0.2

Postoperative Complications.—According to the definition of a febrile postoperative course as a temperature elevation of 100.4° F. orally, 605 patients (Table II) had a fever of one day's duration and 202 had a temperature elevation of 2 or more days. Thirty-seven per cent, or 355 patients, were afebrile following operation. In 84 per cent of the febrile patients the source of the infection seemed to be the operative bed. In 10 per cent of the febrile patients, or 64, a urinary tract infection was responsible. Severe pelvic cellulitis was reported in 7 patients and an infection of the perineal repair occurred in 7 others.

Our gynecologic service has gone through the phase of prophylactic use of bacteriostatic and bactericidal agents in the pre- and postoperative management of our patients. Our first experience was with sulfonamides as prophylaxis against urinary tract infections of the postoperative period. The next step was instillation of sulfonamide powder in the apex of the vagina after operation. Then came the various penicillin preparations and finally the broad-spectrum antibiotics. At the present time we are not using prophylactic antibiotics and feel our incidence of infection has not increased.

In Shaw's[5] experience the most frequent postoperative complication was delayed bleeding on the seventh or eighth day. This was encountered in 4 cases. The most frequent postoperative complication was inability to void after the removal of the retention catheter. This was never mentioned by the early advocates of the Manchester operation. While this is irritating and disturbing to the patient, we feel this difficulty reflects an extensive anterior wall repair and good urinary control can usually be predicted. One hundred forty-six patients, or 15.2 per cent of the series, required an indwelling catheter for 9 or more days. Fifty per cent of the patients were able to void without catheterization after the fifth and seventh postoperative days. The average patient usually required 6 postoperative days before she was emptying her bladder completely. All types of regimens have been tried to prevent this complication but as yet nothing has been found that will work consistently. It is probably better psychology to leave the catheter in place for at least 6 days than to remove it at an early time only to have to reinsert it because of a high residual urine or retention. There were no patients who had permanent difficulty with retention and all were able to leave the hospital without necessity for further catheterization.

There were 7 deaths in the 960 patients subjected to the Fothergill procedure. Some will consider this a very high mortality but one should remember that the older, poor-risk patient was treated by this procedure rather than by vaginal hysterectomy. In this series 58 per cent of our patients were between the ages of 50 and 70 (Table III); thus advanced age is not a deterrent to the Manchester plastic repair. Many of our patients were obese, 17.5 per cent had a hypertension of 150/100 or more, and 5 per cent had diabetes.

TABLE III. AGE DISTRIBUTION OF PATIENTS

AGE RANGE	NO. OF PATIENTS	%
20-29	24	2.5
30-39	115	11.9
40-49	162	16.9
50-59	260	27.0
60-69	299	31.1
70-79	97	10.1
80-89	3	0.3
Total	960	99.8

Considering the advanced age, the medical complications, and the type of patient selected for this procedure, we do not feel the death rate in our series is excessively high. It was probably lower than the anticipated mortality rate had these same patients been subjected to vaginal hysterectomy with repair. Table IV summarizes the pertinent data concerning the patients who died. There were no deaths from hemorrhage. The deaths secondary to myocardial infarction were perhaps unavoidable. The 2 patients who died of pulmonary embolus

presumably had unrecognized phlebothrombosis. The last death occurred in 1953 and this patient perhaps should not have been operated upon since she was definitely a poor-risk patient.

TABLE IV. DEATHS FROM THE MANCHESTER OPERATION

PATIENT	YEAR ADMITTED	AGE	ASSOCIATED ILLNESS AT TIME OF OPERATION	DAY OF DEATH	SYMPTOMS	CAUSE
J. S.	1936	67	Hypertension 160/100	7th	Cyanosis, pulseless	No postmortem ? Myocardial infarction
M. W.	1938	67	Chronic renal disease 10-20 WBC/HPF Specific gravity 1.010	14th	Coma Fever	Postmortem done Uremia Terminal bronchopneumonia
A. O.	1944	56	Severe varicose veins	11th	Chest pain Dyspnea	No postmortem Pulmonary embolus
O. M.	1947	64	Preoperative cystitis	7th	Dyspnea Slow, irregular pulse	No postmortem Myocardial infarction
A. H.	1948	63	Hypertension 240/110 ECG evidence of myocardial disease	7th	Dyspnea Cyanosis Expiratory râles	No postmortem Pulmonary embolus
E. M.	1951	70	Blood pressure 150/90	1st	Cyanosis No pulse	No postmortem Myocardial infarction
M. M.	1953	74	Blood pressure 250/100	4th	Dyspnea No pain	Postmortem Myocardial infarction

Late Postoperative Complications.—The late postoperative results from the Manchester procedure were evaluated both by follow-up examination and letters. Unfortunately, many of our patients could not be examined because of the difficulty of transporting indigent patients. A personal letter was sent to each patient in this series. Fifty-two per cent, or 506 patients, answered the questionnaire. The majority of the patients had complete relief of symptoms and were well satisfied with the postoperative results. A specific question was asked concerning any signs of recurrence of the prolapse. Twenty-two patients, or 4.3 per cent, stated there was evidence of recurring prolapse. Only 11 patients had felt the symptoms severe enough to require further surgery, however. It has been our experience that prolapse of the vaginal vault is much more frequently encountered following vaginal hysterectomy with repair than after a Manchester procedure. In our vaginal hysterectomy series the recurrence rate was over 10 per cent, which is comparable to the experience of others.

Concerning the problem of future malignancy, there has been no case of either epidermoid or endometrial carcinoma occurring after the Manchester procedure. It was previously stated that there was one case of adenocarcinoma of the endocervix present at the time of the operation which recurred 5 months after operation. It is true all of the patients have not been followed but it has been our experience that once patients in Iowa are indigent they remain permanently on relief roles. Thus, if significant recurrence or malignancy had developed, the patient would have been sent to our clinic again for treatment.

A third problem in which we were interested was what happened to the patient who was operated upon before the menopause. Did we affect menstruation adversely? In this group some problems of cervical stenosis and irregular vaginal bleeding were encountered. A significant number of these patients required subsequent dilatation and curettage and a few had to be treated by abdominal hysterectomy to control the bleeding. Although, when the total group of patients is considered, only 2 per cent required subsequent surgery, this is a definite disadvantage and in recent years a vaginal hysterectomy with repair is considered the procedure of choice in the premenopausal patient.

Summary and Conclusions

1. Between the years 1936 and 1955, 960 Manchester-Fothergill operations were performed for genital prolapse at the State University of Iowa Hospitals.

2. The Manchester procedure probably finds its best application in the postmenopausal patient with prolapse.

3. The predominant symptoms of prolapse are the feeling of a bulging mass, urinary hestitancy, and stress incontinence.

4. Considering that vaginal relaxation occurs in the advanced age group, we feel the Manchester procedure is safer than the vaginal hysterectomy with repair.

5. The major postoperative complication of the Manchester operation is urinary retention which is avoided by the use of an indwelling catheter.

6. The recurrence of vaginal relaxation after the Manchester type of procedure is 4.3 per cent as determined by personal follow-up letters. The recurrence rate following vaginal hysterectomy with repair was over 10 per cent in our hospital.

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USE OF THE LOOPED URETERAL CATHETER IN REPAIR OF VESICOVAGINAL FISTULA

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ULLRICH[3] recommended the use of a looped catheter in the bladder to achieve a self-retaining catheter with good drainage. Ellik[1, 2] advocates the use of a looped ureteral catheter for successful extraction of small calculi impacted in the ureter. It is the purpose of this note to describe still another use for the looped catheter.

It is an established principle of vaginal repair of vesicovaginal fistula that traction through the lumen of the fistula with a balloon catheter or other instrument placed inside the bladder is helpful in establishing the necessary cleavage planes before closure. In cases where the fistula is very tiny, it may be difficult to get a sufficiently large Foley catheter or other instrument into the bladder from the vagina.

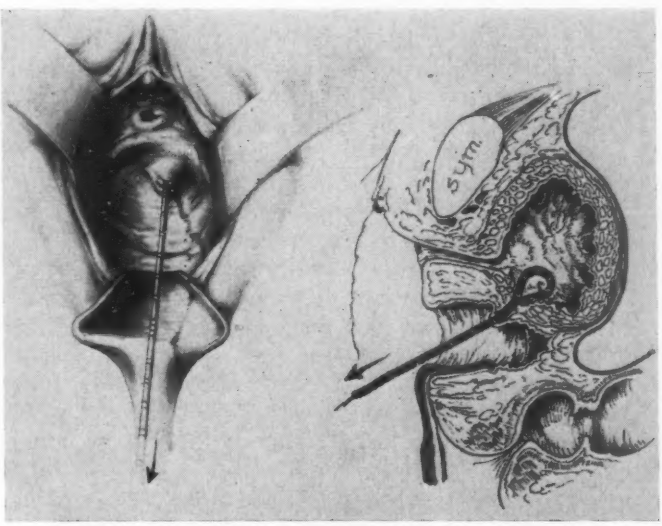

Fig. 1.—Traction on the looped catheter makes the fistula accessible.

We have found it useful to pass Ellik's ureteral catheter through the small vaginal fistula into the bladder. Traction on the wire produces a loop in the end of the catheter and then it is possible by gentle transvaginal trac-

tion to evert the fistula and bring it down into the vaginal field for surgical attack. This simple maneuver makes the fistula more accessible to the surgeon (Fig. 1). It has been used to advantage in 2 cases.

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SURGICAL CORRECTION OF CONGENITAL ATRESIA OF THE CERVIX

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ATRESIA of the cervix may be congenital or acquired, the former being rare and the latter relatively more common. There are three variations of this congenital anomaly, one in which the cervix presents in the vagina but is not canalized, and two in which no cervix appears in the vaginal vault. Of the latter subgroup, one type is characterized by one or two fine tracts connecting the uterine cavity with the vaginal vault, the other by a complete absence of any connection between the vagina and the uterus.

Associated in various combinations with the above are the three anatomical-physiological variables in the uterus itself. The first is characterized by aplasia of the corpus with amenorrhea, offering a diagnostic problem but no urgent need for corrective surgery. Second are the cases with functioning endometrium which result in hematometra. Finally, there are cases in which the channel from uterus to vagina is absent and menstruation proceeds retrograde through the tubes into the pelvic cavity. The case here described falls into this category.

In 1941 Sherwood and Speed[1] reviewed the literature thoroughly and were able to find only 6 cases with the last type of anomaly, to which they added a case of their own. The first reported case was apparently that of Ludwig in 1900, who performed a hysterotomy and forced a trocar down through the cervix into the vagina, but mentioned no follow-up. Bernard and Kernauner resorted to hysterectomy in similar situations. Duyzings reported a case in which the operation consisted of incising the cervix and placing a drain in it, but again no follow-up was reported.

The first successful operation which achieved a permanent channel from the uterus into the vagina was performed by Portes in 1938. His operation consisted essentially in bypassing the cervix and anastomosing the vagina with the endometrium. Engelhens in 1939 changed the procedure slightly by excising the solid cervix and then anastomosing the vagina with the endometrium. He had to reoperate and excise a little more of the lower uterine segment in order to get a larger opening for his anastomosis, which then proved successful. Sherwood and Speed modified Engelhen's procedure by using a stem pessary for several weeks after operation to maintain an open channel, and reported a successful 3 year follow-up.

The case reports of Majekodunmi,[2] Putterman,[3] and Sanford[4] are illustrative of unusual situations which have occurred with the type of anomaly wherein only a channel connects the uterine cavity with the vagina and pregnancy intervenes to bring the anomaly to light.

The final 2 cases in which plastic surgery was both indicated and successfully carried out were one performed by Maliphant[5] in 1948 and the one herein reported, performed in 1956. In Maliphant's case the cervix presented in the vagina, but was solid throughout its course except for a shallow dimple on the portio. He resected the solid portion, anastomosed the vagina to the endometrium, and maintained the new canal with an indwelling catheter. Two years afterward the patient was menstruating regularly and was free of any pain.

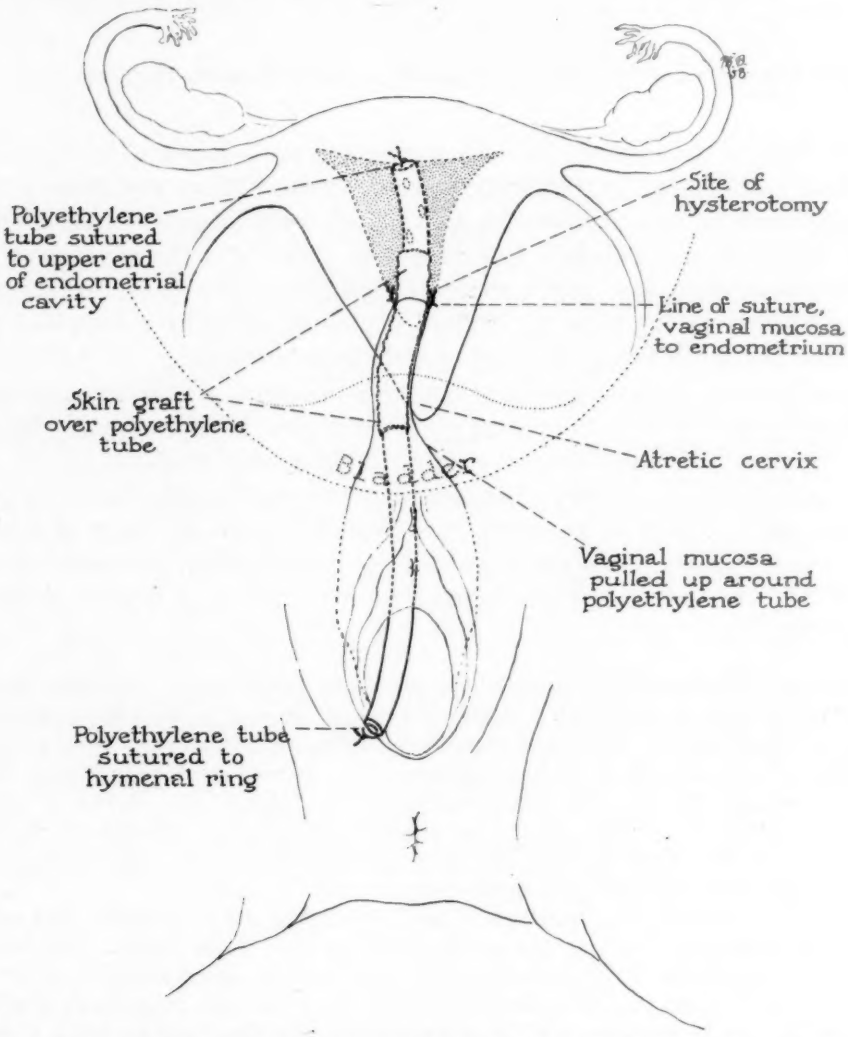
Polyethylene tube sutured to upper end of endometrial cavity
Site of hysterotomy
Line of suture, vaginal mucosa to endometrium
Skin graft over polyethylene tube
Bladder
Atretic cervix
Vaginal mucosa pulled up around polyethylene tube
Polyethylene tube sutured to hymenal ring

Fig. 1.—Anterior view showing completed repair with polyethylene tube in place.

The following case is the fifth to be added to this series. It is essentially a bypass operation such as that first described in 1938 by Portes but with some modifications.

A 16-year-old girl was first seen in August, 1955, with the chief complaints of primary amenorrhea and monthly episodes of cramping, becoming progressively more severe during the previous 3 years.

Examination showed a normal girl except for a right direct inguinal hernia, a slightly shortened vagina, and no cervix visible to inspection. There was no tract leading from the vaginal vault up to the uterine cavity. The right ovary was enlarged to about 2 inches in diameter.

The first operation corrected the hernia and the right corpus luteum cyst was excised. An attempt to fashion a new channel through the underdeveloped cervix and to maintain it with a small polyethylene tube, which came out spontaneously after 3 weeks, proved a failure, however. The channel promptly closed up and could not be located by a probe the day following the loss of the catheter. This illustrates a very important point, namely, that, if a successful result is to be achieved, the solid cervix must either be amputated or bypassed by the plastic procedure.

At the second operation, the bypass procedure (Fig. 1) was selected because of the possibility of hemorrhage from the prominent uterine arteries and veins which were present just lateral to the hypoplastic cervix.

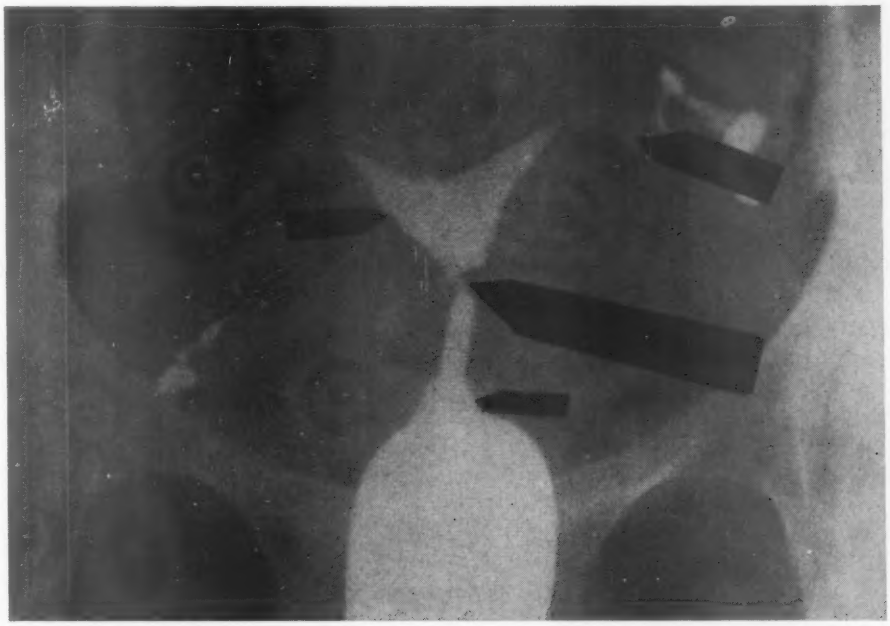

Fig. 2.—Anteroposterior hysterosalpingogram showing reconstructed uterovaginal channel, vagina, uterus, and patent tubes.

A review of the important steps in the second operation follows: The entire anterior surface of the uterus and cervix together with the vaginal vault was exposed by reflecting the bladder downward. With an assistant probing the vaginal vault from below, the proper point of incision into the vagina was located. A 1½ inch hysterotomy presented no problem from the standpoint of excessive bleeding. The ¼ inch polyethylene tube was placed in the uterus, secured in the upper end of the uterine cavity with a chromic 0 suture, and the other end pushed down into the vagina through the opening in the vaginal vault.

The next step was the anastomosis of the opening in the vaginal vault with the endometrium over the polyethylene tube, which was done without difficulty. The hysterotomy was closed in the usual fashion and the bladder sutured back in normal position. At the end of the operation the lower end of the polyethylene tube was sutured with silk to the vaginal opening. The polyethylene tube was covered with a split-thickness graft which could act as an extra factor to insure epithelization at the point of anastomosis should the vaginal mucosa have pulled loose from the endometrium.

The polyethylene tube came out on the nineteenth postoperative day. The patient's newly formed channel was probed periodically, starting about 3 weeks after the tube came out. The probings were a bit difficult at the point of anastomosis for about 3 months. They were performed with progressively less frequency for 1½ years.

Approximately 4 months after operation a hysterosalpingogram was performed which visualized the new tract. In Fig. 2 the uterine cavity with the newly created tract may be seen as it enters the vagina. The tubes are both patent.

The patient has continued in excellent health for a little over 2 years after her second operation. Her periods were scanty and lasted 2 to 3 days at first, but have progressed to a painless 4 day period 2 years later.

Summary

A case is presented of congenital occlusion of the cervix, in which a permanent channel was constructed by anastomosing the endometrium of the lower uterine cavity to the vagina over a polyethylene tube.

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ADENOMATOID TUMORS OF THE UTERUS AND ADNEXA

Report of Eleven Cases

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THE literature concerning benign tumors of the uterus and adnexa is voluminous. The adenomatoid tumor, however, is seldom mentioned in gynecologic writing. Probably many will not be aware of this special benign tumor, or will feel that it strictly belongs to the male genitourinary organs. Though by no means common, adenomatoid tumors have been reported in the uterus, tube, and ovary.[6]

Occurrence

The actual incidence, though small, is undoubtedly greater than reported. This tumor usually masquerades as a leiomyoma and, thus, evades microscopic study. Ragins and Crane[8] reviewed 7,485 Fallopian tubes removed at the Cook County Hospital and found only 3 adenomatoid tumors, an incidence of 0.04 per cent. There were 3,471 hysterectomies performed at Emanuel Hospital, Portland, Oregon from 1950 through 1956. Five uteri (0.14 per cent) were diagnosed as having adenomatoid tumors. Fajers[4] reviewed the literature in 1949 and found 25 cases. Horn and Lewis,[6] in a 1951 review, studied 25 cases and added 5 of their own. Table I gives the details of 11 previously unreported adenomatoid tumors from the records of the Portland Sanitarium and Emanuel Hospital.

Clinical Aspects

There is no characteristic clinical picture because these small tumors do not cause symptoms. They are discovered, unsuspected, at autopsy or in the examination of surgical specimens. When they are detected in tissues removed at operation, other major pathologic lesions are almost always present. It was interesting to note that the majority of pathologic descriptions studied in the preparation of this paper began with "surprisingly" or " an unsuspected finding is." Pathologists, experienced with gross tumor morphology frequently missed the true nature of the lesion macroscopically. Thus there is little wonder that the tumor is not suspected clinically.

Age and parity seem to have no bearing on the incidence or size of adenomatoid tumors.

Gross Description

Horn and Lewis[6] found the majority reported to be in the uterus, with the tube the next most common site. Most of ours are in or near the uterine

TABLE I

IDENTIFICATION	AGE	GRAVIDITY	PARITY	RACE	PRESENTING SYMPTOMS	ASSOCIATED PATHOLOGIC LESIONS	LOCATION OF TUMOR	SIZE	OPERATION PERFORMED
PS No. 45162	39	0	0	White	Pelvic pressure	Multiple leiomyomas	Cornu	Not known	Subtotal hysterectomy
PS No. 373724	46	x	0	White	Uterine bleeding	Endometrial hyperplasia, endometriosis	One in each cornu	1 cm. 1.2 cm.	Total abdominal hysterectomy; bilateral salpingo-oophorectomy
EH No. C72890	54	ii	ii	White	Painful intercourse, vaginal mass	Chronic cervicitis	Cornual area	Not known	Total abdominal hysterectomy
EH No. C70627	44	i	0	White	Irregular menses, intermittent bleeding	Endometriosis, adenomyosis, leiomyomas	Anterior fundus	1.2 cm.	Total abdominal hysterectomy
EH No. C84657	46	i	i	White	Pelvic pain, heavy menstruation	Endometrial polyp, adenomyosis, leiomyomas	Right cornual area	1.0 cm.	Total abdominal hysterectomy
EH No. C80306	43	iii	iii	White	Irregular menses	Cystic hyperplasia of endometrium	Apex of fundus	1.3 cm.	Total abdominal hysterectomy
EH No. C02796	44	i	i	White	Irregular menses	Leiomyomas	Apex of fundus	2.0 cm.	Total abdominal hysterectomy
EH No. E13105 1957	37	0	0	White	Nodular enlarging pelvic mass	Leiomyoma	Apex of fundus	4.5 cm.	Total abdominal hysterectomy
PS No. 37220	41	ii	ii	White	Pelvic pressure	Multiple leiomyomas	Isthmus of tube	1.6 cm.	Total abdominal hysterectomy
EH No. C89049	41	ii	ii	White	Heavy menstruation	Lymphangiectasis of uterus, leiomyoma, hyperplasia of endometrium	Right tube, center	0.1 cm.	Total abdominal hysterectomy, right salpingo-oophorectomy
EH No. E13432 1957	49	iv	iii	White	Irregular menses, lower abdominal pain	Adenomyosis, hyperplasia of endometrium, leiomyomas	Tube	Microscopic	Total abdominal hysterectomy, bilateral salpingo-oophorectomy

cornu. Only 3 were located in the tube. All previously reported lesions were single. One uterus in this series, however, had an adenomatoid tumor in either cornual area (Fig. 1). None have been detected in the cervix or vagina, and they are infrequent in the ovary.[6] Their presence usually causes a protuberance, but in the uterus this may be very subtle. A few are completely hidden in the myometrium. They are small, usually between 0.5 and 2 cm. The largest, by far, in our series was 4.5 cm.

Rounded and well demarcated, they seem grossly encapsulated. Actually, only a pseudocapsule is present. The color ranges from gray white to frank yellow. There are no hemorrhages and the cut surface seems to bulge. They have a finely fibrous appearance and feel somewhat firmer than the surrounding muscle.

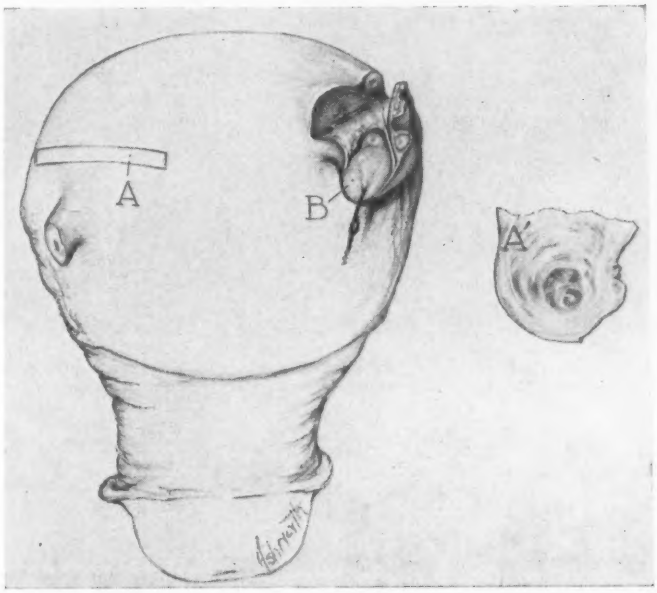

Fig. 1.—Gross description: *A* represents the subtle adenomatoid tumor deep in the myometrium. *B* is the more common type that produces a protuberance on the surface. All previous examples reported are single.

Microscopic Description

The microscopic picture is primarily one of low columnar cells arranged in solid cords or forming acini and ducts. The supporting tissues are varying amounts of smooth muscle, interspersed with collagen connective elements. At the periphery, the supporting structures condense slightly to form a pseudocapsule. Some of the channels present seem to be large vacuolated cells. These are present as thin-walled, empty areas with a nucleus displaced to one side. All degrees of this development, from signet-ring cells to thin-walled channels, can be seen. Actual vascular elements vary in these tumors, but certainly account for few of the vessellike structures. Scattered lymphocytic infiltration is occasionally seen. Mitoses are infrequent. The surrounding normal tissue is not markedly compressed, a point that Golden and Ash[5] feel is in favor of slow growth. Evans[3] found that these growths stain negative for fat, but positive for mucin. A brush border described by Fajers[4] was noted primarily on the cuboidal cells. Fig. 2 depicts well the varied histologic structure so common to these growths.

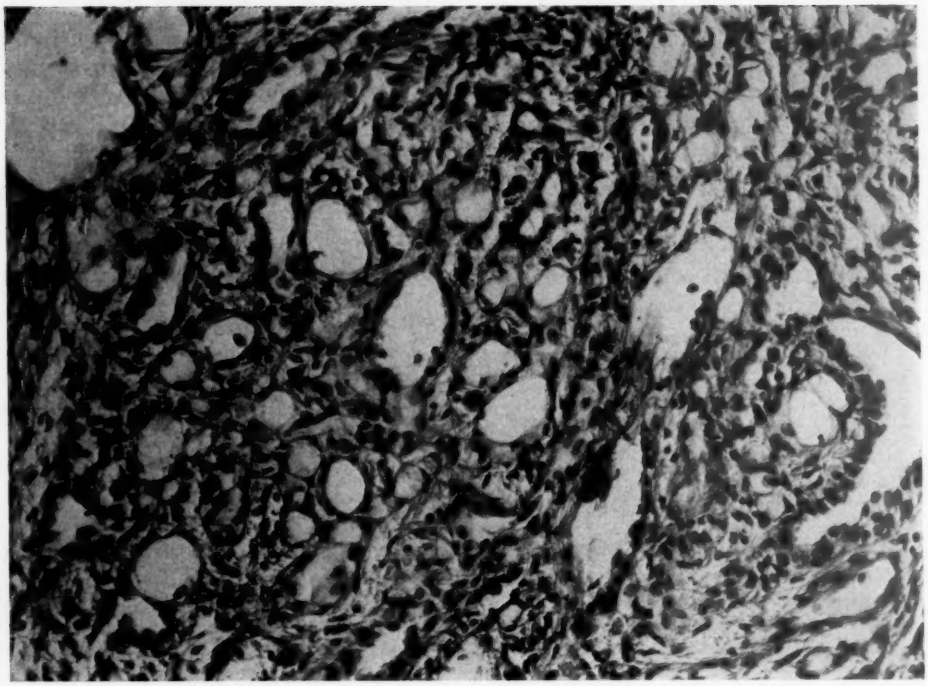

Fig. 2.—Microscopic description: Ductlike structures lined with cuboidal cells are interspersed by thin-walled channels. Signet-ring cells can be seen. The stroma is not dense. (×240; reduced ¼.)

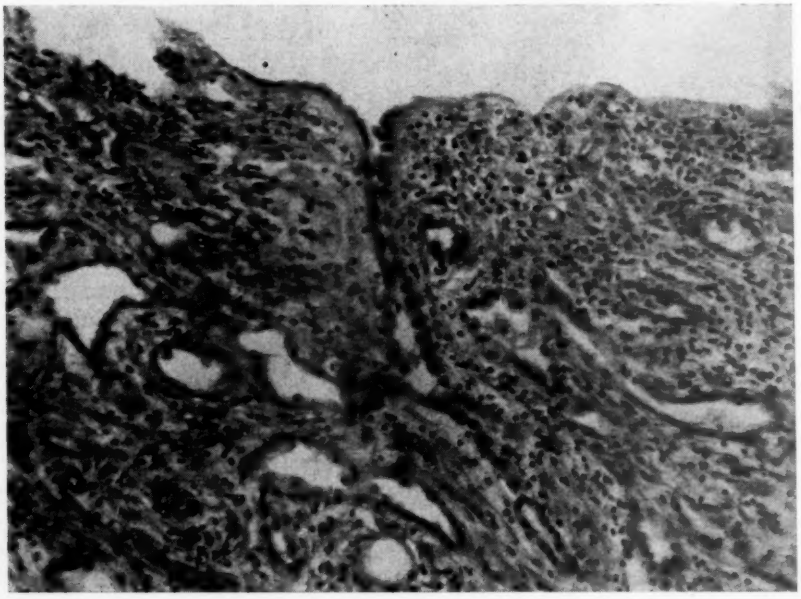

Fig. 3.—This is a duct from an adenomatoid tumor opening onto the surface of the uterus. (From Evans: Am. J. Path. 19: 461, 1943.)

Comment

The adenomatoid tumor is more important for what it is not, than for what it is, since it can easily be mistaken for adenocarcinoma and is frequently diagnosed grossly as leiomyoma. There have been reports of massive tumors of the ovary[9] and tube[1] which some[4, 6] felt to be of this type. Aschheim[1] reported a part-solid, part-cystic tumor the size of a child's head that he called a lymphangioma of the tube. His presentation, however, was with slides and the microscopic description in the text is very scanty. It is difficult to include this case in the adenomatoid group. Rice, Pearson, and Treadwell[9] reported a malignant lymphangioma of the ovary measuring 15 by 12 by 7 cm. This has been included by some also, but because of its size and malignancy it is probably another neoplasm.

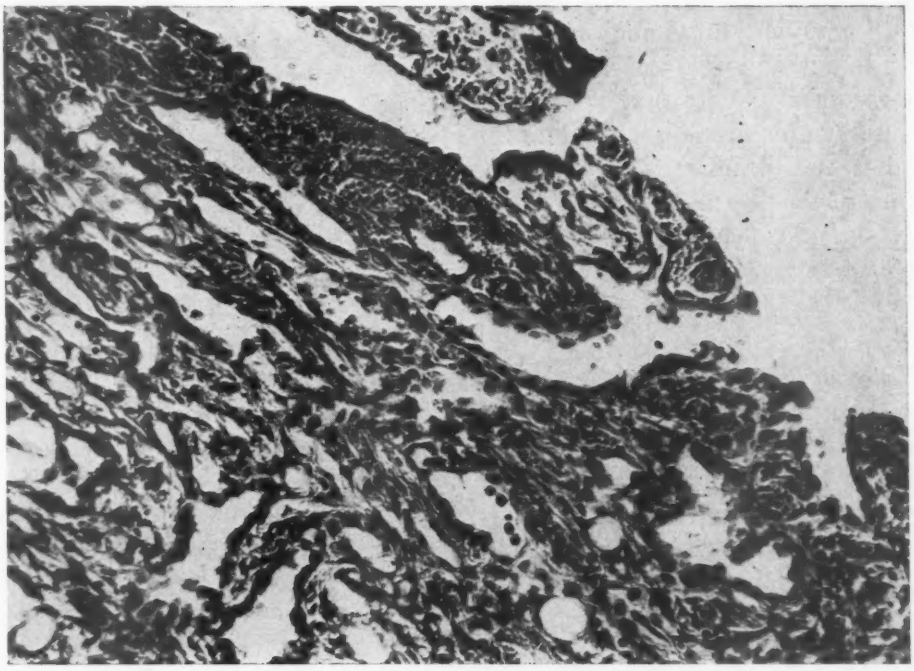

Fig. 4.—Photomicrograph demonstrating three ducts apparently opening onto the surface of the uterus. This is a section from the tumor *B* in Fig. 1. The serosal aspect is the area where the ducts open. (×240; reduced ¼.)

The histogenesis of the adenomatoid tumor is not settled. Many sources have been suggested: epithelial structures, endothelial elements, and Müllerian remnants, but all have been discredited.[2-5] There are several[3, 4, 6] who favor mesothelium as the origin. Evans[3] presented a photomicrograph (Fig. 3) showing a duct of one tumor opening onto the surface of the uterus. He also felt that, histologically, mesonephric structures had no essential similarity to adenomatoid tumors. Fajers[4] stated that the distribution of the tumors was incorrect for mesonephric origin and described an instance where, in one of his own cases, mesothelial cells dipped into the uterine capsule. Fig. 4 is

from one of our cases. In it, three separate ducts can be seen apparently opening onto the surface of the uterus. In other parts of the same specimen, there were more ducts oriented toward the serosa of the uterus. Horn and Lewis[6] supported mesothelial origin because of the "frequency with which the secretion of mucicarminophilic material can be demonstrated."

Dixon and Moore[2] cast doubt on the mesothelial origin because adenomatoid tumors are all benign while most tumors originating from pleura and peritoneum are malignant. Longo, McDonald, and Thompson[7] considered adenomatoid tumors "hamartomas" of the mesonephros. They stated that mesothelium-lined peritoneal surfaces are extensive, and yet adenomatoid tumors are not described away from the embryologic course of the mesonephros.

Sneeden[10] holds that the morphology is entirely compatible with a mesonephric origin. In his study of the mesonephric duct and its relationship to certain cervical malignancies, he has demonstrated a mesonephric duct opening into an endocervical gland. The evidence of ducts from adenomatoid tumors opening onto and being in continuity with the serosa of the uterus does not, in his opinion, eliminate the mesonephros as the origin. He believes, but has not demonstrated, that the mesonephric duct may open onto the surface of the uterus.

Golden and Ash[5] delineated no origin, but supported the term "adenomatoid," which they stated is "morphologically correct and genetically neutral."

Summary

Eleven examples of a special benign tumor of the female internal genitals have been presented. The general characteristics of adenomatoid tumors have been noted. Pertinent gross and microscopic descriptions with representative examples of morphology are submitted. A discussion of the two major possible origins, though inconclusive, is given. It is hoped that others will be stimulated to study and report their observations as to the probable mode of origin of adenomatoid growths.

Addendum.—Very recently the possibilities of origin of adenomatoid tumors have been reviewed in detail by J. R. Jackson.[11]

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HILUS-CELL AND GRANULOSA-CELL TUMORS IN THE SAME OVARY

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MASCULINIZATION of the female is one of the most startling syndromes in all of medicine. When it occurs, usually in association with amenorrhea, the individual may be found to have an unusual ovarian tumor as the primary cause of her condition. In contradistinction to feminizing mesenchymomas, which secrete female hormone, the masculinizing tumors present a much more complex picture and are usually more difficult to diagnose preoperatively.

The patient (H. S.) was a white nullipara who first consulted a private physician at the age of 18 because she had never had a normal menstrual period. Cyclic hormone therapy was administered, which produced scanty menstruation at more or less regular intervals. Amenorrhea resulted as soon as medication was discontinued. Several years later, at the age of 26, the patient was referred to the Gynecological Clinic of the Lafayette Charity Hospital, Lafayette, Louisiana. Careful history revealed that she had had increasingly excessive growth of body and facial hair since the age of 18 years and had been in the habit of shaving her face regularly for about 2 years. On examination it was noted that the patient exhibited a masculine physical habitus. There was a mustache and a small amount of chest hair. The distribution of pubic hair was masculine. The clitoris (Fig. 1) was enlarged. The vagina was normal. The cervix was normal and the uterus was anterior and of normal size. No pelvic masses were palpated.

The patient was admitted to the hospital. The urinary 17-ketosteroids were found to be elevated to 27.5 mg. per 24 hours. Study of sections of epidermis showed the genetic sex to be female. A posterior colpotomy was performed on Oct. 25, 1955. The pelvis appeared to be normal. The ovaries were small and were not thought to be unusual on gross examination; however, routine biopsies were made.

Microscopic examination showed a peculiar pattern of calcification of primordial follicles in the cortex of both ovaries. In addition, the specimen from the left ovary contained a small portion of a granulosa-cell tumor, as well as an aggregation of Leydig-like cells suggesting a separate tumor.

The signs of masculinization in this patient were considered to be caused by the ovarian tumor, although its exact pathological nature had not been established. While feminizing mesenchymomas have been found to produce masculinization,[1, 2] the diagnosis of granulosa-cell tumor as the sole lesion did not seem adequate. The slightly elevated urinary 17-ketosteroids seemed to indicate that either an adrenal lesion or a separate Leydig-cell tumor of the ovary[3] was present. Other possibilities considered were pseudohermaphroditism and true hermaphroditism. Since female sex chromatin was present and the cause of the masculinization obscure, it was thought proper to perform a laparotomy,

to remove the affected ovary and to explore the adrenals. This was carried out on Feb. 28, 1956. The internal genital organs appeared grossly normal to the operating surgeon. No abnormalities were found on palpation of the adrenal gland areas.

Gross pathological examination of the ovary showed no abnormality. Section across its mid-portion, however, revealed a small, firm, yellow, circumscribed nodule in the medullary and hilar regions.

Fig. 1.—External genitals with enlarged clitoris.

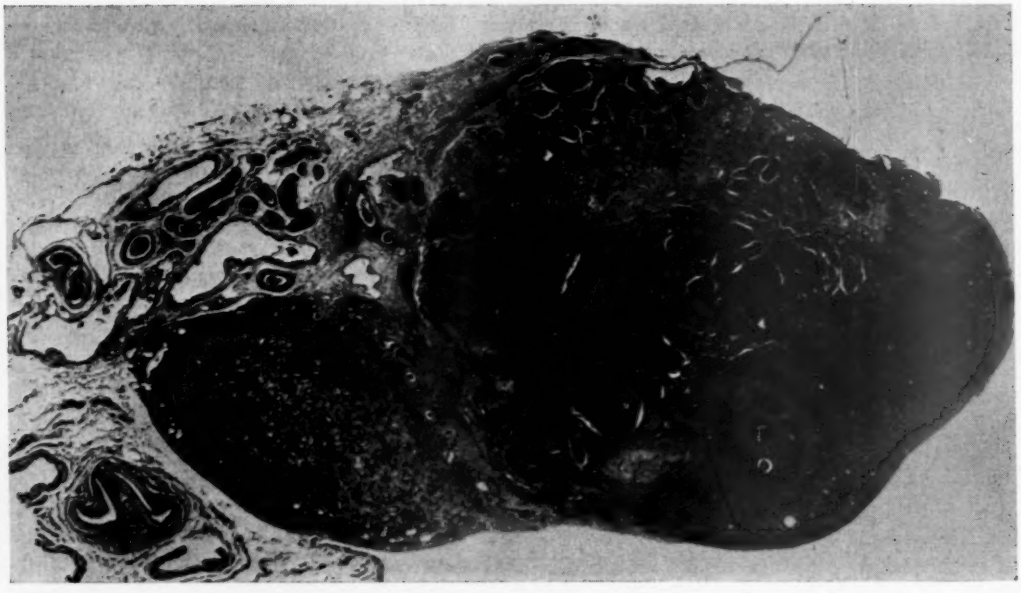

Fig. 2.—Cross section of ovary showing two separate tumors, one in the medullary part of the ovary and the other in the mesovarium. (×12; reduced ⅙.)

Under low magnification of the entire cross section (Fig. 2), two separate tumors were seen, although this had not been evident grossly. The one located in the center of the ovary was made up of round or elongated masses of cells separated by the fibrous

stroma of the tumor and ovary itself. Under higher magnification, these masses were revealed to be granulosa-cell tumor (Fig. 3). It was noted that masses of granulosa cells occupied sites in the ovarian cortex very close to the surface, suggesting invasion. The second tumor was more clearly encapsulated and lay within the mesovarium next to the hilum.

Fig. 4 shows the cell make-up of this tumor. There are two types of cells, large clear cells and smaller ones with more dense eosinophilic cytoplasm. This detail is illustrated in Fig. 5. Both resemble the hilus cells found in the normal ovary, the smaller cells more than the larger ones.

Close study of the cortex disclosed two unusual features. The first was the presence of large polyhedral cells, distributed at random, which were similar to the hilus cells but which also resembled luteinized cortical stroma cells—the so-called thecosis of ovarian cortex. There were areas where these cells merged with the granulosa-cell tumor. In this context it seemed reasonable to suppose that these polyhedral cells were luteinized stromal cells. Other areas exhibited almost identical cells adjacent to clusters of undoubted hilus cells.

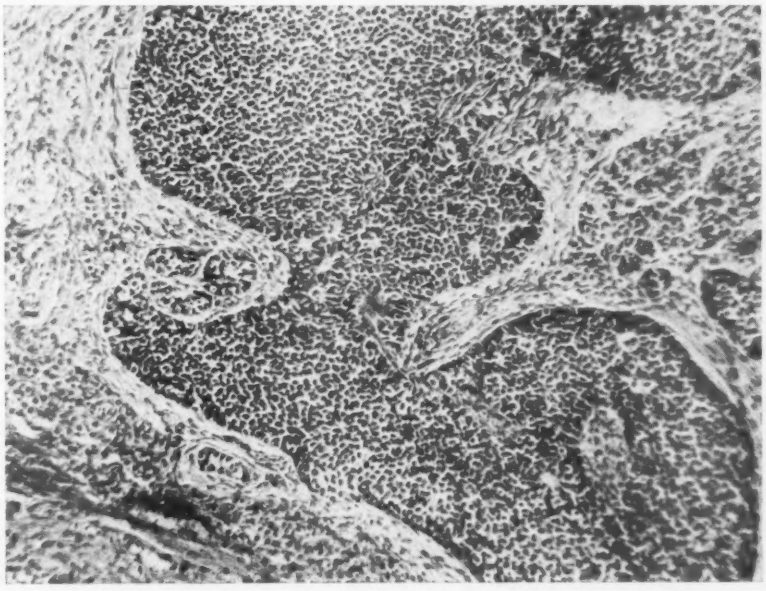

Fig. 3.—Typical granulosa-cell tumor within the ovary. Low power.

The other unusual feature of the cortex of the ovary was the presence of small foci of calcium scattered throughout. Most of these seemed to be embedded in the cortex at random, while some were surrounded by a layer of cells of the type which surround the primordial ovum, suggesting that the calcification had taken place in primordial follicles. There were a few primordial follicles intact in some of the sections, and an occasional ovum was seen.

Histologically, the granulosa-cell tumor was typical, and occupied a position quite apart from the other growth. Similarly, the hilus-cell adenoma was circumscribed and made up of the characteristic cells. It was because of these two features—anatomically separate masses and cytologically typical components—that the decision was made in favor of two neoplasms, granulosa-cell tumor and hilus-cell tumor.

Gynandroblastoma was considered. This term, however, designates a specific entity and not a heterogeneous combination of separate tumor elements,[4] and would require that

there be one mass with component parts or cells more intimately arranged. Sertoli-Leydig cell tumors have been observed in ovary[5, 6] and in animal testes, but descriptions of them indicate they are not comparable to the tumors of this patient.

The cells of the adenoma were large, polyhedral, and lipid bearing. The morphological similarity to interstitial testicular cells (Leydig) helped to identify them as the

Fig. 4.

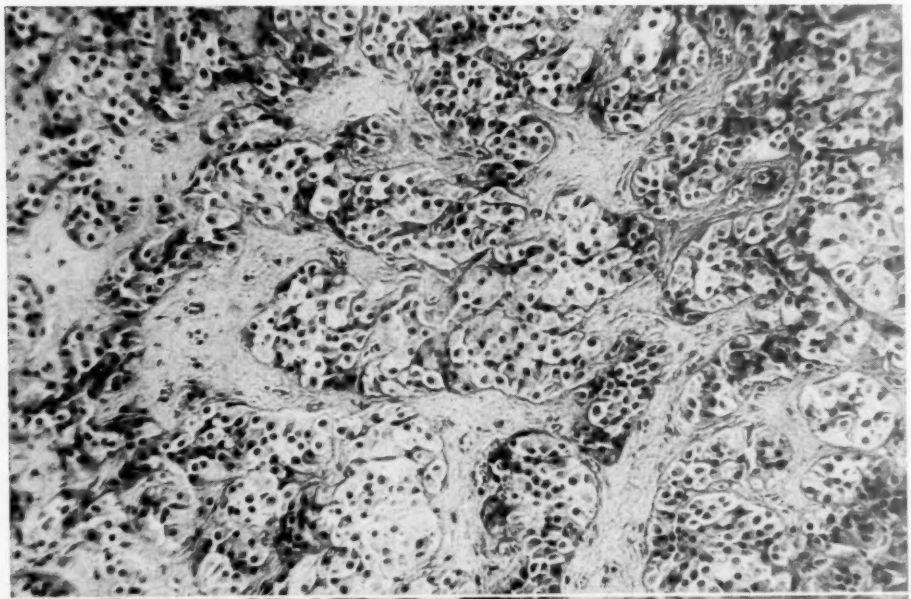

Fig. 5.

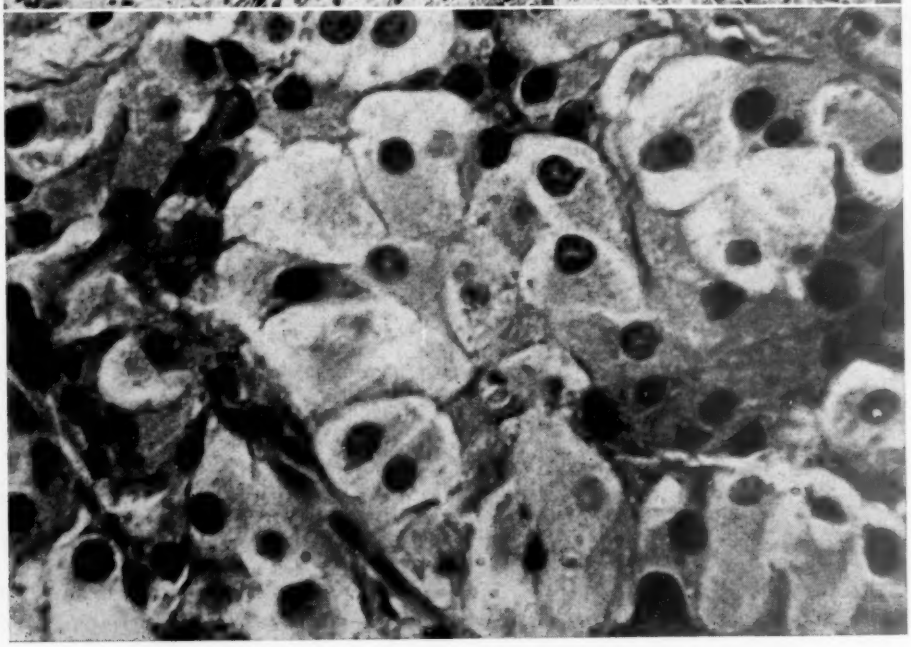

Fig. 4.—Hilus-cell adenoma in mesovarium. Low power.

Fig. 5.—Component cells of the adenoma are of two types, large clear cells and smaller, more darkly stained cells. High power.

type found in the ovarian hilus.[7, 8] Similar cells were seen in the ovarian cortex and the hilar region; to surmise, however, that there was a hyperplasia of these cells prior to the appearance of the adenoma would seem to be highly speculative.

Follow-up examinations of the patient through December, 1957, showed partial regression of the signs of masculinity, although there was still some growth of facial hair. Several examinations of urinary 17-ketosteroids were performed, the average being 11.9 mg. per 24 hours.

Comment

In an attempt to determine the possible origin of the hilus-cell tumor, a study of the genetic sex of its cells was carried out. It was exceedingly interesting to us to find that female sex chromatin was present in the nuclei of these cells.* It seems, therefore, that the tumor did not develop from embryonic rests of genetically male cells. It may be assumed that the cells of this tumor secreted male hormone even though they were actually female from a genetic point of view. It has been pointed out by others that even in the normal ovary the hilus cells may produce androgens.[10]

One other point bearing on origin may be worth commenting upon. The finding of polyhedral cells in the ovarian cortex which were morphologically and spatially related to both granulosa cells and hilus cells could indicate that both tumors originated from cells of the ovarian cortex.

We gratefully acknowledge the consultation and contributions given to us in the study of this patient by Dr. Howard Jones, Johns Hopkins University, Dr. Albert Segaloff, Ochsner Foundation Hospital, Dr. Murray Barr, University of Ontario, Dr. R. F. Ranson, Lafayette Charity Hospital, and the late Dr. Emil Novak of Baltimore, Maryland.

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*We are grateful to Dr. Murray Barr,[9] who reviewed a section of the tumor and agreed with this finding.

LABORATORY AND CLINICAL STUDIES ON VAGINAL TRICHOMONIASIS

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THREE divergent views concerning the pathogenicity of *Trichomonas vaginalis* are: (1) that it is definitely pathogenic, (2) that it acts symbiotically with associated bacteria, and (3) that it is a harmless saprophyte.[3] Even though it is well known that *T. vaginalis* often occurs in women in the absence of symptoms or apparent pathologic conditions,[12] the experimental production of typical *T. vaginalis* vaginitis by inoculation of bacteria-free strains into the vaginas of volunteers as done by Trussell and Plass[13] indicates that, at least under certain circumstances, this parasite is pathogenic. This view is strengthened by the observations of Kessel and Gafford,[6] of subepithelial cellular infiltrations and other pathologic alterations in the mucosa of women with vaginal trichomoniasis. In addition, de Allende and Orías[5] reported changes in the proportions of various cell types in the vaginal epithelium, and Papanicolaou and Wolinska[9] described alterations in vaginal smears attributable to *T. vaginalis.*

The factors which are responsible for the variable pathologic effects of infection with *T. vaginalis* are not adequately understood. The present report is based upon a series of clinical and laboratory studies on alterations associated with *T. vaginalis* in women with vaginal trichomoniasis, before, during, and after treatment of this infection. Similar studies also were done on women not infected with *T. vaginalis.*

Methods of Procedure

Clinical and laboratory studies were conducted on 60 white and 40 Negro women. Seventy-four agreed to participate in the studies when *T. vaginalis* was reported during a collaborative survey with the National Cancer Institute, 23 were referred to the project because of vaginal discharge and/or itching of the genitals, and 3 without trichomoniasis volunteered for comparative studies on infected and noninfected women.

Clinical Observations.—All women participating in the study were interviewed, with particular attention to the history of vaginal complaints, and a complete physical examination was done, with especial attention to the appearance of the vaginal and labial mucosa, the urethra, the various glands, and

the amount and character of any discharge present. The participation of 30 of the women was limited to one examination. The remaining 70 had from one to 101 additional examinations, most of which comprised inspection of the intralabial area including the urethra, Skene's glands, and the distal portion of the vagina made visible by spreading the vaginal introitus with the fingers. When it was desired to see deeper into the vagina a Pederson bivalve speculum which caused less discomfort than the Graves speculum was usually employed.

Laboratory Examinations.—Two samples of vaginal secretion were obtained at each clinic visit by means of a sterile curved glass pipette equipped with a strong rubber bulb.[5, 10] The first pipette sample was rinsed into a tube of NIH trypticase liver serum medium[3, 4] for demonstration of *T. vaginalis* and/or fungi. The content of the second pipette was used to prepare 4 smears, 2 of which were immediately fixed in equal parts of ether and absolute ethyl alcohol and were subsequently stained by Shorr's[11] method for study of the proportion of the various cell types. The other 2 were permitted to dry in the air, one was stained by Mack's[7] method over Lugol's solution for determination of the proportion of cells containing glycogen, and the other by Gram's technique for bacteria. When bacterial cultures were desired, they were obtained before any of these procedures and usually by means of swabs inserted between the blades of a sterile unlubricated speculum. In some instances part of the secretion in the first pipette was expelled into a tube with nutrient broth for bacterial culture before being rinsed in the TLS medium for culture of the Trichomonas.

For more precise information on cyclical changes during menstrual cycles, 17 of the women cooperated by taking smears each day from themselves. To obviate the danger of self-inflicted injury through breakage of glass pipettes, a kit containing disposable plastic straws was provided.

Results and Comment

Clinical Observations.—The signs and symptoms of vaginal trichomoniasis have been described in detail by numerous authors.[3, 12] Our observations were in general agreement with these findings. Examinations for trichomonads were consistently negative, however, in 2 patients with the classical frothy discharge which is ordinarily considered pathognomonic of infection with *T. vaginalis.*

TABLE I. SUMMARY OF HISTORY OF DISCHARGE AND PRURITUS AND FINDINGS OF VAGINAL INFLAMMATION IN 100 PATIENTS ON FIRST CLINIC VISIT

INFECTION	NO. OF PATIENTS	HISTORY OF VAGINAL DISCHARGE	HISTORY OF GENITAL PRURITUS	INFLAMMATION AT VAGINAL INTROITUS*
Trichomonas only	65	57	37	40
Trichomonas and fungus	13	8	4	6
Fungus only	12	11	9	9
Neither Trichomonas nor fungus	10	6	6	3
Total	100	82	56	58

*Includes degrees of inflammation not ordinarily considered of clinical significance.

As shown in Table I, the majority of women admitted the presence or history of a vaginal discharge. There was little correlation between the findings on examination and the patient's complaints of a discharge. Over half

stated that they either had or had had pruritus of the genitals and approximately an equal number when first seen had definite objective evidence of mild to severe inflammation of the vaginal introitus. Inflammation of the vault of the vagina was less common than inflammation at the introitus. There appeared to be an excellent correlation between the degree of inflammation noted at the vaginal introitus and the severity of subjective symptoms described by the patient.

TABLE II. OCCURRENCE OF MILD TO SEVERE INFLAMMATION AT THE VAGINAL INTROITUS IN WOMEN WITHOUT TREATMENT FOR AT LEAST ONE MONTH WHO WERE FOLLOWED THREE MONTHS OR LONGER

INFECTION AT FIRST EXAMINATION	TOTAL PATIENTS EXAMINED	PATIENTS WITH INFLAMMATION AT VAGINAL INTROITUS					
		FIRST EXAMINATION		LATER EXAMINATION		TOTAL WITH INFLAMMATION	
		ALL DEGREES	SEVERE ONLY	ALL DEGREES	SEVERE ONLY	ALL DEGREES	SEVERE ONLY
Trichomonas	40	20	4	32	13	37	16
Fungus only	7	4	1	4	2	5	3
Neither Trichomonas nor fungus	5	1	0	2	1	3	1
Total	52	25	5	38	16	45	20

The majority of our patients with trichomoniasis were not particularly disturbed by the symptoms even if they admitted their presence, and had never consulted a physician concerning them. A few, in fact, stated that they joined the project in the hope that our findings would benefit others rather than in the expectation of personal improvement. As shown in Table II, however, nearly every patient who was followed over a period of several months had one or more episodes of mild to marked inflammation at the vaginal introitus which almost invariably was accompanied by increased itching or other sensations.

In addition, 19 patients with trichomoniasis had exacerbations of vaginitis while under treatment, although all such women also had similar episodes unrelated to therapy. Most of these occurred during treatment with Aureomycin. Vaginal fungi of various genera and species often were cultured for the first time during these exacerbations.

Laboratory Data.—

Vaginal cornification: The relationship of trichomoniasis to changes in the vaginal epithelium has been noted by a number of investigators. de Allende and Orías[5] and Papanicolaou and Wolinska[9] reported an increase in the number of cornified cells in the vaginal smears from women with vaginal trichomoniasis.

Calculations of the per cent of cornified cells were made on a total of 300 smears from 33 patients with trichomoniasis who had received no treatment for at least 2 months and on 236 smears from 5 women without *T. vaginalis.* The average count was computed for day 5 through day 28 of the menstrual cycle, with the first day of the menses counted as day one. As shown in Fig. 1, *A,* these two curves do not resemble normal ovulatory cycles and do not differ significantly from one another. Deviation from the normal of the women without trichomoniasis is not surprising since 2 of the 5 joined the study because of vaginal complaints.

Readings also were obtained on 237 smears from 24 patients during or within one month after vaginal treatment with Aureomycin or Propion Gel,

either alone or together. The curve plotted from the daily average of these readings, Fig. 1, *B*, shows 40 to 55 per cent cornified cells during the first and fourth weeks of the menstrual cycle. These figures are in excess of the probable normal range of cornification.[5] Similar readings on 328 smears from 26 patients treated with other drugs* showed average percentages of cornified cells fluctuating between 36 and 48 per cent. Even these levels were higher than those found in the untreated women with trichomoniasis. It thus appeared that an increase in the percentages of cornified cells resulted from the treatments. This increase was apparent, both early and late in the menstrual cycle, when percentages are usually low. The effect was especially marked and persisted longest with Aureomycin.

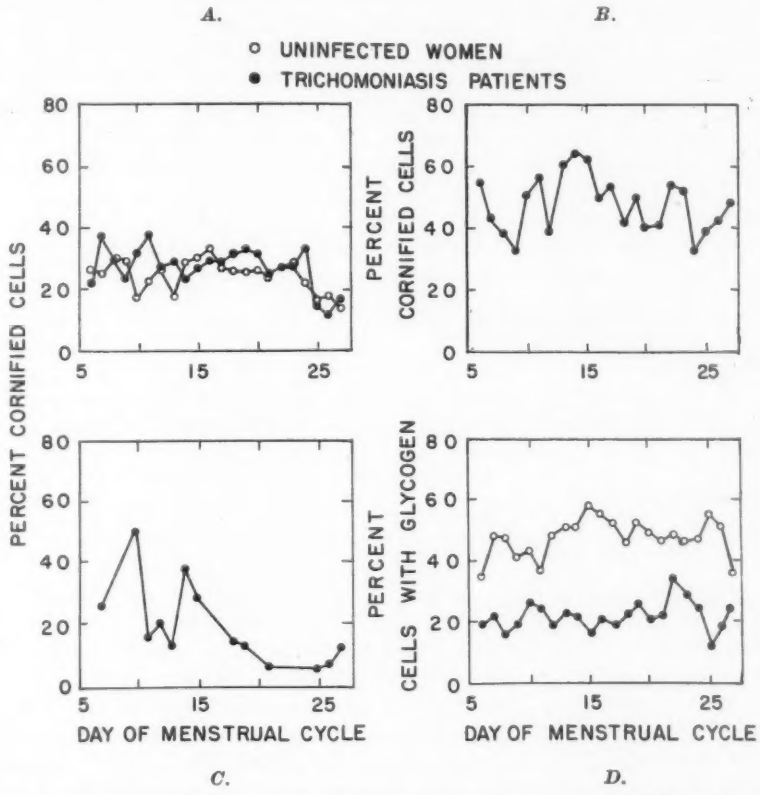

Fig. 1.—Vaginal cornification and glycogen curves from women with and without *Trichomonas vaginalis*.

A, Average per cent of cornified vaginal cells in women who had no treatment for at least 2 months.

B, Average per cent of cornified vaginal cells during and one month after treatment of trichomoniasis with vaginal Aureomycin and/or Propion Gel.

C, Average per cent of cornified vaginal cells after cure of vaginal trichomoniasis.

D, Average per cent of vaginal cells with glycogen in women who had no treatment for at least 2 months.

The averages of 98 readings on 9 cured trichomoniasis patients gave the curve shown in Fig. 1, *C*. Improvement in cyclical cornification, if present, was not marked. The question whether the results shown were attributable to eradication of the flagellates has not been answered.

The classification of the cornification curves prepared from daily smears submitted by 17 patients is given in Table III.

*Colpotabs, Floraquin, Milibis, Terramycin, Trichofuron, Tritheon, and Vagisec.

TABLE III. CLASSIFICATION OF CORNIFICATION CURVES PREPARED FROM DAILY VAGINAL SMEARS BY 17 PATIENTS

TYPE OF CURVE	TRICHOMONAS INFECTION	FUNGUS INFECTION	NEITHER INFECTION
Eutrophic	0	0	3
Hypotrophic	10	2	4
Dystrophic	3	0	0
Persistent high cornification	1	0	2
Distorted by prior therapy	3	0	0
Total cycles	17	2	9

Deep cells: Deep cells are very scanty in vaginal smears except from patients with atrophic epithelium when the numbers of such cells are used to grade the degree of atrophy.[5] A very much higher proportion of vaginal smears from patients with moderate to severe vaginitis contained deep cells than those from women with a minimal or without vaginitis. This was especially true when the vaginitis was accompanied by an intense vaginal leukocytosis. Similar findings (Table IV) also were observed in women without *T. vaginalis.*

TABLE IV. OCCURRENCE OF INTENSE LEUKOCYTOSIS AND DEEP CELLS IN VAGINAL SMEARS OF WOMEN WITH AND WITHOUT VAGINAL TRICHOMONIASIS

	DEGREE OF VAGINITIS PRESENT					
	MODERATE TO SEVERE			MINIMAL OR ABSENT		
		% OF SMEARS			% OF SMEARS	
INFECTION	NO. OF PATIENTS	WITH LEUKOCYTOSIS	WITH DEEP CELLS	NO. OF PATIENTS	WITH LEUKOCYTOSIS	WITH DEEP CELLS
Trichomonas	15	28	49	20	8	22
Fungus only	1	75	60	2	0	15
Neither Trichomonas nor fungus	1	41	38	4	4	21

Vaginal glycogen: The data failed to demonstrate a cyclical fluctuation in the per cent of cells containing glycogen such as described by Mack[7] and Bernstine and Rakoff.[3] On the other hand the data illustrated in Fig. 1, *D*, offered considerable support for the observations of Mack,[8] that *T. vaginalis* is associated with "glycogen poverty" and the experiments of Asami and Nakamura,[1] indicating that the flagellate may appreciably lower the glycogen content of the vagina. The average glycogen index from 260 smears from 31 women with *T. vaginalis* who had received no treatment for at least 2 months fluctuated between 10 and 25 per cent, with a slight peak to 34 per cent on the twenty-second day of the cycle. Similar computations from 169 smears of 10 women who had been cured of trichomoniasis showed appreciably higher fluctuations, between 30 and 45 per cent, while those from 199 smears from 7 women without either trichomoniasis or candidiasis were still higher, between 35 and 57 per cent. Curves from the women with trichomoniasis who furnished daily smears showed that the percentages of cells with glycogen were low, usually lower than those of cornification. On the other hand, the curves from women without trichomoniasis showed appreciably higher percentages of glycogen, usually above those of cornification. These studies thus showed that women with vaginal trichomoniasis had a lower level of vaginal glycogen than uninfected women.

Bacterial flora: Although subject to exception under certain conditions, a close correlation has been shown between bacterial flora and the state of

health of the vagina.[3] Most investigators have adopted a classification in which three types of vaginal flora are recognized.[3, 12]

Grade I. Döderlein's bacilli (gram-positive rods) alone are present.

Grade II. Döderlein's bacilli are present together with one or several other types of bacteria.

Grade III. Döderlein's bacilli are not present; the vaginal flora consists of various other bacteria.

During the sexually active period of life the Grade I flora is considered as "healthy" or normal and Grade III to be indicative of a pathologic condition.

Analysis was made of 583 gram-stained vaginal smears of 54 women who had received no medication during the preceding month. The vast majority of smears from the uninfected women had a Grade I bacterial flora (Table V) and Lactobacillus (Döderlein's bacillus) was demonstrated in all cultures made from this group (Table VI). Nearly all vaginal smears from women with *T. vaginalis* showed a mixed flora; however, Lactobacillus was demonstrated in nearly half of the cultures. Comparison of gram-stained smears before and after cure of trichomoniasis in 11 patients (Table VII) showed a great increase in the proportion of smears indicating a Grade I flora. Cultures, however, did not indicate any marked increased frequency of Lactobacillus.

TABLE V. OCCURRENCE OF GRADE I BACTERIAL FLORA IN WOMEN WHO HAD RECEIVED NO MEDICATION FOR AT LEAST ONE MONTH

INFECTION	NO. OF PATIENTS	NO. OF SMEARS	SMEARS WITH GRADE I FLORA	
			NO.	%
T. vaginalis	40	260	31	12
Fungus only	7	94	44	47
Neither infection	7	104	95	91

TABLE VI. OCCURRENCE OF LACTOBACILLUS IN WOMEN WHO HAD RECEIVED NO MEDICATION FOR AT LEAST ONE MONTH

INFECTION	NO. OF PATIENTS	NO. OF CULTURES	CULTURES WITH LACTOBACILLUS	
			NO.	%
T. vaginalis	18	51	24	47
After cure of *T. vaginalis*	6	21	12	57
Fungus only	4	27	19	70
Neither	5	17	17	100

TABLE VII. OCCURRENCE OF GRADE I BACTERIAL FLORA BEFORE AND AFTER CURE OF VAGINAL TRICHOMONIASIS

INFECTION	NO. OF PATIENTS	NO. OF SMEARS	SMEARS WITH GRADE I FLORA	
			NO.	%
Trichomoniasis	11	94	8	9
Cured	11	125	48	38

Cultures of vaginal secretion for predominating organisms showed little difference between patients with *T. vaginalis* with minimal or absent vaginitis and women without *T. vaginalis*, except that the latter had a much higher proportion of Lactobacillus. Cultures from patients with *T. vaginalis* vaginitis, however, had a much higher proportion of nonhemolytic *Staphylococcus albus* and Group D Streptococcus than either of the other groups of women (Table VIII).

TABLE VIII. BACTERIA REPORTED FROM CULTURES OF VAGINAL MATERIAL FROM INDICATED CASES, BY THE LABORATORY OF CLINICAL PATHOLOGY

BACTERIA	SOURCES OF SPECIMENS							
	TRICHOMONIASIS WITH MARKED VAGINITIS		TRICHOMONIASIS WITH MINIMAL VAGINITIS		TRICHOMONIASIS "CURED"		WITHOUT TRICHOMONIASIS*	
	NO.	%	NO.	%	NO.	%	NO.	%
Lactobacillus	11	46	13	48	8	50	17	77
Staphylococcus albus								
hemolytic	2	8	8	30	4	25	9	41
nonhemolytic	15	63	7	26	2	13	5	23
S. aureus	3	13	1	4	0	--	0	--
Streptococcus A	2	8	7	26	1	6	0	--
B	0	--	1	4	0	--	0	--
D†	17	71	12	44	5	31	4	18
G	1	4	4	15	1	6	5	23
Coliform group‡	17	71	19	70	10	63	7	32
Diphtheroids	9	38	5	19	7	44	8	36
Pseudomonas sp.	1	4	0	--	0	--	0	--
Bacteroides	2	8	2	7	1	6	2	9
Hemophilus sp.	1	4	1	4	0	--	0	--
Bacillus subtilis	2	8	1	4	3	19	1	5
Bacterium anitratum	1	4	1	4	0	--	0	--

*Includes four patients with a fungus infection.
†Includes Enterococcus.
‡Includes *Escherichia coli, Aerobacter aerogenes,* Paracolon, Proteus sp. and Klebsiella.

Summary

1. The present report is based upon a series of clinical and laboratory studies during the past 3 years on women with vaginal trichomoniasis, before, during, and after treatment of the infection, in an endeavor to furnish information on alterations attributable to *T. vaginalis.*

2. Over half of the patients when first seen had mild to severe inflammation of the vaginal introitus but not necessarily of the vaginal vault.

3. Even though the majority of the patients had not been sufficiently disturbed by their vaginal symptoms to consult a physician prior to joining the study, nearly every patient who was followed over a period of several months had one or more episodes of mild to marked inflammation of the vaginal introitus which was almost invariably accompanied by increased itching or other sensations. This amounted to a definite clinical vaginitis in 40 per cent of the patients which, however, usually improved after a few days even without treatment.

4. Calculation of the fluctuations in per cent of cornified cells during menstrual cycles failed to demonstrate any marked difference between women with or without *T. vaginalis* and did not show evidence of an increased percentage of cornified cells in women with vaginal trichomoniasis.

5. Administration of trichomonacidal and fungicidal medication, however, resulted in an increased per cent of cornified cells which was most pronounced and persisted the longest with vaginal Aureomycin.

6. A greater proportion of vaginal smears from women with moderate to severe vaginitis had deep cells and intense leukocytosis than those from

women without such an inflammation, but there was no particular difference between women with or without *T. vaginalis.*

7. The per cent of vaginal cells containing glycogen was appreciably lower in women with *T. vaginalis* than in women from whom the parasite had been eradicated and was even higher in the women who had never had such an infection.

8. Grade I bacterial flora was observed in only 12 per cent of vaginal smears from patients with *T. vaginalis.* Lactobacillus was, however, cultured from approximately 50 per cent of such patients.

9. Following cure of trichomoniasis, a great many more smears were of Grade I type but cultures with Lactobacillus were not appreciably increased.

10. Cultures of vaginal secretion showed little difference between patients with *T. vaginalis* with minimal or absent vaginitis and women without *T. vaginalis,* except that the latter had a much higher proportion of Lactobacillus. Cultures from patients with *T. vaginalis* vaginitis, however, had a much higher proportion of nonhemolytic *Staphylococcus albus* and Group D Streptococcus than either of the other groups of women.

We wish to thank Dr. Ernest Singer, visiting scientist in the Clinical Pathology Laboratory, Clinical Center, National Institutes of Health, for assistance in the bacteriological analyses.

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A NEW TREATMENT OF TRICHOMONAS VAGINITIS

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THERE are few gynecological conditions more annoying and more difficult to treat than Trichomonas vaginitis. It is estimated that its incidence in the women in the United States approximates 20 per cent. Much has been written about the various and different attempts to establish a therapy that would go beyond amelioration of symptoms. There is developing gradually a new approach to the treatment and eradication of this disease. It is based on the concept that Trichomonas vaginitis is a contagious disease, carried and transmitted chiefly by the male sexual partner. Many investigators, therefore, feel it is justified to classify trichomoniasis as a venereal disease.[1, 2] Until and unless immunization is possible, definite prophylactic measures such as the use of condoms, at least during the course of therapy in the female, have the same importance in the eradication of this disease as the elimination of endogenous extravaginal foci of infections.

In view of past therapeutic failures, Davis and Grand[3, 4, 5] postulated the following requirements for a satisfactory trichomonacide: ability to penetrate and dissolve mucinous materials; failure to irritate already inflamed tissues; failure to irritate already inflamed tissues; ability to kill the organism in less than 3 mnutes. As a result, they developed a combination of three surface-acting agents: a chelating agent (sodium ethylene diamine tetra-acetate) to remove the calcium of the calcium proteinate in the trichomonad's cell membrane; a wetting agent (sodium dioctyl sulfosuccinate) to lower the surface tension and to remove lipids; a detergent (polyoxyethylene nonyl phenol) to denature the protein. The present clinical investigation has been undertaken to test the efficacy of this preparation.*

Material and Methods

Fifty-eight women were included in this series: 45 private and 13 clinic patients. The age range was 19 to 55 years. The diagnosis of Trichomonas vaginitis was based on the well-known clinical picture and identification of the organism.[6] Among the important signs and symptoms[1, 2, 7] were foamy, malodorous discharge, erythema and minute hemorrhages of the vaginal mucosa and sometimes of the portio, edema of the vulva, burning and pruritus vulvae, intertrigo, dyspareunia, and dysuria.

In some cases, a microscopic examination of the vaginal mucosa was carried out. Diffuse subepithelial infiltrations with lymphocytes and plasma cells

*Available as Vagisec liquid and jelly; supplied by Julius Schmid, Inc., New York.

were found. In the acute stages there were polymorphonuclear leukocytes. Areas of hemorrhage, necrosis, and shallow ulceration were seen. The surface of the vaginal mucosa was covered with particulate matter, trichomonads, and blood cells.

In order to confirm the diagnosis, all patients were instructed not to douche on the day of examination. A drop of discharge was taken from the posterior fornix by a wire loop. Mixed with several drops of warm isotonic saline, it was examined immediately under the microscope. The *Trichomonas vaginalis* is easily identified.[8] It is a clear, actively motile, flagellated protozoan, 10 to 30 μ by 5 to 15 μ, with four flagella projecting anteriorly and an axostyle posteriorly. Pus and other debris are often seen adhering to the axostyle.

The course of therapy included both office and home treatment. During the office visit an unlubricated vaginal speculum was inserted, and a cotton ball saturated in Vagisec solution (1:100 dilution) was applied to the entire vaginal canal, while the speculum was turned from side to side. After 3 to 4 minutes' washing, the vagina was dried. This was done twice weekly for 3 weeks. Pregnant patients received the same treatment.

Nonpregnant patients were instructed to douche at home with Vagisec solution (1:250 dilution in warm tap water) daily, and then to instill 5 c.c. of Vagisec jelly at bedtime, for 3 weeks. Pregnant patients used the jelly, but not the douche.

Treatment did not necessarily extend through the menstrual period. If the period coincided with the 3-week course, then the use of the douche during menstruation was stressed. If, however, the 3-week course was concluded before menstruation, it was not extended to include the period.

The 3-week course of therapy was chosen (instead of the recommended 4-week course) because experience shows that the length of time required for such treatment is an important factor for the patient. In our opinion, as evidenced in this investigation, a 3-week course of therapy with Vagisec liquid and jelly is sufficient to achieve satisfactory results, provided the treatment is carried out regularly and properly, and the endogenous and exogenous sources of infection are eliminated.

In each case a complete pelvic examination was performed (Table I). Before the vaginal therapy was started, extravaginal foci of infection were sought and eradicated, instead of local therapy alone, and, in case of failure, other courses of treatment were given. Debris and tissue necrosis were cleaned up, and associated purulent infections were treated with antibiotics.

TABLE I. ASSOCIATED OBSTETRICAL AND GYNECOLOGICAL CONDITIONS

	NO. OF CASES	CURED OF TRICHOMONAS VAGINITIS	FAILURES
Pregnancy	8	6	2
Fibromyomas of the uterus	8	8	0
Cystorectocele	5	5	0
Vaginismus	1	1	0
Carcinoma of cervix	1	0	1
Unhealed episiotomy	1	1	0
Retrodisplacement	1	1	0
Total	25	22	3

The husbands were advised that sexual intercourse accounted for most cases of reinfection.

In order to follow the patient's progress, a wet smear was taken at each office visit. The criterion of cure, however, was the negative culture taken

1 to 3 days after each of the next three menses following completion of the 3-week course of therapy. Cultures were taken after the patient was instructed not to douche for 3 days previously. The culture method of Kupferberg[9] was used.

Results

Of the 58 patients who completed the required 3-week course of home and office treatment, 54 were considered cured. Many patients have been followed up by taking cultures for as long as 8 months after completion of the 3-week course of treatment, and all of these cases have remained negative. The 4 failures were, we feel sure, due to lack of cooperation, either of the patient or her husband.

Table II indicates the number of treatments that were necessary to obtain a negative smear. These figures are identical with the number of treatments necessary for relief of symptoms.

TABLE II. NEGATIVE SMEAR OBTAINED

NO. OF TREATMENTS	NO. OF PATIENTS
1	55
2	2
3	1
Total	58

It should be mentioned that 35 patients had this condition for at least 6 months to 5 years (Table III), and 44 patients had received previously at least one complete course of therapy with various other preparations (Table IV).

TABLE III. DURATION OF SYMPTOMS PRIOR TO START OF THERAPY

	NO. OF PATIENTS	CURES	FAILURES
One month or less	4	4	0
Six months or less	19	18	1
One year or less	23	21	2
Two years or less	7	7	0
Five years or less	5	4	1
Total	58	54	4

TABLE IV. PREVIOUS TREATMENT WITH OTHER PREPARATIONS

	NO. OF PATIENTS	CURES WITH VAGISEC
At least one complete course of treatment	44	43
Sporadic treatments	2	0
No previous treatments	12	11
Total	58	54

Comparison With Other Trichomonacidal Agents

In view of these very favorable results achieved by using Vagisec liquid and jelly in the treatment of vaginal trichomoniasis, it may be of interest to the clinician to see some comparative data on other forms of treatment. As far as we know, most investigators conducting studies on the better-known and popular trichomonacidal preparations rarely use cultures as the criterion

for "cure." Therefore, in our opinion, the word "cure" in these studies signifies "clinical cure" rather than "parasitological cure." Illustrative of such reports are those listed below.

A report on the use of a vaginal suppository and powder,[10] containing N-(5-nitro-2-furfurylidene)-3-amino-2 oxazolidone, states that 97.9 per cent of the patients using this preparation for one week had no actively motile trichomonads in the vaginal smears. Another report on a vaginal suppository and powder,[11] containing bismuth glycolyl arsanilate shows a similarly high "cure rate" (81 per cent), with the negative hanging drop as criterion. The hanging drop test method was employed in a study on a vaginal jelly and liquid,[12] containing 5-amino-1,3-bis(beta-ethylhexyl)-5-methylhexahydropyrimidine. After 3 weeks of treatment the hanging drops of 88 per cent of the patients became negative. The use of a vaginal jelly containing 9-aminoacridine hydrochloride, sulfanilamide, allantoin, and lactose, resulted in 82.5 per cent "bacteriologic cure."[13] A promising oral tablet, containing 2-acetylamino-5-nitrothiazole, "eliminated trichomoniasis in approximately one-third of women whose marital partners were not treated."[14] In this study the criterion of cure was the culture. When both partners were treated the "cure rate" went up to 70 per cent, according to a personal communication.[15]

An examination of high "cure rates," as in this short review of other methods of treatments, usually reveals a very liberal concept of the criterion for "cure." Faced with this lack of a rigid standard of "cure," the physician becomes hesitant and reluctant in his choice of therapy.

Summary

A series of 58 cases of Trichomonas vaginitis was treated with Vagisec liquid and jelly in order to test the efficacy of these preparations. There were 54 successful cases, or 93.1 per cent, as proved by negative cultures obtained in 3 consecutive months after completion of the therapy. Though this series is small, we feel these are very encouraging results in the treatment of a condition which is extremely difficult to cure.

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THERAPEUTIC EXERCISES FOR TEEN-AGE DYSMENORRHEA

A Statistical Comparison of the Billig and Mosher Techniques in the Philadelphia School System

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THERE have been many suggestions for the treatment of the symptom complex of dysmenorrhea. Among them are various special exercises, the performance of which is said to lead to cure of the pain. The two commonly utilized techniques have been those of Mosher[1] and Billig.[2]

Mosher, one of the first to preach liberation of women from constrictive clothing, was an advocate of regular planned physical exercise. The purposes of the special exercises she proposed for dysmenorrhea are the stimulation of circulation and the relief of pelvic and leg congestion. The exercises are divided into three components: breathing, leg, and abdominal. They should be performed twice daily as follows:

1. In the hook-lying* position, with one hand placed on the abdomen, the girl breathes deeply ten times.
2. In the standing position, with the hands resting on the top of the back of a chair, the girl raises and lowers the heels twenty times.
3. In the same position as in 2, the girl bends the knees deeply and extends them five times.
4. In the hook-lying* position, the girl brings her knees as close to the chest as she can, and then returns to the hook-lying position. This exercise is done ten times.

Billig, an orthopedist, assumed that dysmenorrheic pain is produced by a postural defect and by "contracted ligaments." He advised a series of stretching exercises. Originally the patient was placed in a prone lying position on a flat table, the pelvis immobilized and the legs passively hyperextended and adducted. From that procedure have developed the current Billig exercises which are performed three times daily, six times on each side in the following manner:

1. Starting position: The girl stands with her left side toward a wall. Her feet are together and about 18 inches from the wall, the actual distance depending upon the length of the upper arm from the elbow to the shoulder. The left forearm and hand are placed against the wall

*Supine position with the knees bent and the soles of the feet flat on the mat.

at shoulder level. The heel of the right hand is placed in the hollow on the posterior aspect of the greater trochanter of the femur. The girl should strongly contract the abdominal and gluteal muscles as the pelvis is tilted upward in front and downward in back.

2. The exercise: The pelvis is moved obliquely forward toward the wall to a point of restriction, and then a little beyond. This movement is aided by the heel of the hand which presses on the greater trochanter of the femur. The shoulders should be kept in line with the elbow which is resting against the wall, and not permitted to shift forward. The knees remain straight, while the pelvis never touches the wall if the exercise is performed correctly. The exercise is to be done three times to the left side. The position is then reversed and the exercise done three times to the right side.

Method of Study

By the use of a questionnaire, 5,324 girls with dysmenorrhea from 19 Philadelphia Junior High, Senior High, and Vocational Schools were requested to state whether their dysmenorrhea was "cured," improved, unchanged, or worse following the employment of Billig or Mosher exercises for 6 months to 2 years. Physical education teachers helped the students fill out the questionnaire and kept the records of follow-up. The study ran over a period of more than 8 years, from September, 1948, until January, 1957. "Cure" was said to result when there had been no pain for at least 3 consecutive months as of the last known status.

Approximately 90 per cent of the girls in the series had had their menarche at 11 to 13 years of age. Three fourths had regular cycles, usually at monthly intervals; one fourth had irregular cycles. Many of the girls had been referred for exercises by the school nurses. Some students volunteered. It is estimated that approximately three fourths of these girls had severe dysmenorrhea; one fourth had mild or moderate dysmenorrhea. Of those classified as having severe dysmenorrhea, 81 per cent complained of pain predominantly in the lower abdomen and pelvis, 9 per cent of unilateral lower abdominopelvic pain, 7 per cent of pain involving the entire abdomen and pelvis, and 1 per cent of upper abdominal pain. Only 2 per cent complained of pain predominantly elsewhere (back, thighs, or legs).

Results

It was felt that percentages should not be computed for any school with fewer than 20 girls participating, since percentages based on small numbers can be quite misleading. In view of past experience with school-to-school differences, it was also considered important to compare the two exercises within each school.

In five schools, the Billig only was used; in eight schools, both exercises were performed but fewer than 20 girls participated in one or the other (usually the Mosher).

In six of the nineteen schools there were at least 20 girls who performed the Billig and at least 20 who performed the Mosher exercises. The results with respect to cure or improvement in 1,270 girls who took the Billig exercises and in 340 girls who practiced the Mosher exercises are outlined in Table I. After taking the Billig exercises an average of 74 per cent per school were "cured" or improved; the corresponding figure for the Mosher exercises is 76 per cent. The difference of 2 percentage points is not significant.

TABLE I. PER CENT OF GIRLS "CURED" OR IMPROVED WITH BILLIG AND WITH MOSHER EXERCISES FOR DYSMENORRHEA

SCHOOL	BILLIG		MOSHER	
	NUMBER OF GIRLS WITH DYSMENORRHEA	% "CURED" OR IMPROVED	NUMBER OF GIRLS WITH DYSMENORRHEA	% "CURED" OR IMPROVED
C	332	91	56	89
E	283	86	28	92
L	288	74	104	81
M	45	75	29	65
R	230	61	77	61
S	92	58	46	65
Total	1,270	74*	340	76*

*Unweighted mean of school percentages.

When, within each school, data were analyzed for all students regardless of the type of exercise (Billig or Mosher), the average "cure" or improvement rate for all nineteen schools was 78 per cent per school. There was a highly significant school-to-school difference (probability of chi square less than 0.001) with "cures" and improvement combined, ranging from 60 to 100 per cent (Table II).

TABLE II. RESULTS AFTER SPECIAL EXERCISES FOR DYSMENORRHEA (BILLIG OR MOSHER)

SCHOOL	NUMBER OF GIRLS WITH DYSMENORRHEA	"CURED" (%)	IMPROVED (%)	UNCHANGED (%)	WORSE (%)
A	29	10	90	0	0
B	336	61	35	4	0
C	388	27	64	7	2
D	543	17	72	9	2
E	311	13	74	12	1
F	623	11	74	15	0
G	368	42	42	15	1
H	331	38	44	16	2
I	136	24	58	17	1
J	292	19	60	19	2
K	266	11	67	21	1
L	392	16	60	18	6
M	74	18	54	27	1
N	534	16	56	25	3
O	153	14	55	31	0
P	71	7	59	34	0
Q	32	6	60	28	6
R	307	16	45	37	2
S	138	22	38	38	2
Total	5,324	20*	58*	20*	2*

*Unweighted mean of school percentages.

Comment

The literature contains confirmation of the effectiveness of the Mosher exercises by Bell and Parsons[3] and of the Billig exercises by Haman[4] and Dick and associates.[5] But from our results it is rather surprising how the results from the Billig and Mosher exercises parallel the results of the treatment of dysmenorrhea by other methods. According to Henriksen,[6] "good results" were obtained in 79.2 per cent of patients treated by a wide variety of procedures.

When the "cured" and improved groups were combined, there were highly significant school-to-school differences. Differences among schools may be attributed to differences in definition of dysmenorrhea, unavoidable differences in teaching and performing the exercises, and, probably most important, differences in the enthusiasm of instructors and students. This is why unweighted means* of the school percentages were used. On the average however, 78 per cent per school were either cured or improved and only 2 per cent became worse. The over-all average was 20 per cent "cured"; this is practically the same as the per cent of cases that resolved without treatment in a previously reported study.[7] Hence, there is no evidence that the exercises affected the rate of total "cures" at all. Since there is no control group, we cannot say definitely that even the improvement rate is affected by the exercises. It seems unlikely to us, however, that as many as 78 per cent would have been either "cured" or improved if the exercises had no effect whatsoever. Further studies are necessary in this respect.

Since the cure and improvement rates are quite similar with different modes of therapy, why should one use special exercises in the treatment of dysmenorrhea? There are some obvious advantages. The exercises can be taught to large groups of girls at school; there is no expensive medication; the exercises are certainly to be preferred to surgical procedures; they can be continued over long periods of time and can be repeated. From our data it appears that there is no difference in results between the Billig and the Mosher exercises. The Billig exercise is to be preferred since it requires less time and less floor space than the Mosher exercises (though it does require more wall space). Currently a new set of exercises is being evaluated. These exercises are easier to teach, supervise, and perform than either of the above and may prove to be at least as effective.

Summary

1. During a period of more than 8 years, 5,324 girls of nineteen Philadelphia Junior High, Senior High, and Vocational Schools were treated for dysmenorrhea by either the Billig or Mosher exercises.

2. Both exercises gave approximately the same results. On the average, more than three fourths of the girls were either "cured" (complete absence of symptoms for at least the last 3 months of follow-up) or improved. This rate varied from school to school and ranged from 60 to 100 per cent.

3. The over-all average of "cure" per school was 20 per cent. This is practically the same per cent of cases that, in a previous study, resolved without any therapy.

4. Although there is no specific evidence in our study that exercises affect the rate of total cures, they seem to offer a simple easy approach for at least partial relief of dysmenorrhea.

*Obtained by adding the column of percentages and dividing this total by the number of schools (regardless of varying numbers of students per school).

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DEPARTMENT OF CURRENT OPINION

Clinical Problems

CYTOSMEARS

Case Presentation

Mrs. K. A. S., aged 51 years, a widow, never pregnant, presented herself without symptoms for a routine gynecologic examination on Jan. 25, 1957. Examination: The vulva and vagina were normal; a large polyp filled the external os; the portio of the cervix was normal; the uterus was anterior, of normal size, freely movable, and regular in contour; the adnexa were normal. Cytosmear: Atypical squamous cells; one malignant squamous cell. Clinical diagnosis:

1. Cervical polyp
2. Atypical cytosmear

Jan. 28, 1957.	Operation: Pelvic findings are as listed. Procedure: Polypectomy, curettage, high cervical conization. Pathology report: Cervical polyp, chronic endocervicitis, secretary endometrium.
Mar. 22, 1957.	No symptoms are present. The cervix is normal. The uterus and adnexa are normal. Cytosmear: Strongly suggestive of malignancy. Operation: Conization, curettage. Pathology report: Hyperactive cervical squamous epithelium (no malignancy), chronic cervicitis.
May 6, 1957.	No symptoms. Cervix, uterus, and adnexa are normal. Cytosmear: Atypical squamous cells.
June 11, 1957.	No symptoms. Cervix, uterus, and adnexa are normal. Cytosmear: Positive for squamous-cell cancer.
July 12, 1957.	No symptoms. Cervix, uterus, and adnexa are normal. General physical examination revealed no abnormalities. Cytosmear studied in a different laboratory was also positive for squamous-cell cancer.

Problem: What is the possible significance or interpretation of the findings and what is your recommended management?

Consultation

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The case under discussion is unusual and that is why it is a very interesting one for comments.

This situation is encountered rarely, but the negative findings, after a positive Papanicolaou smear, are evidence that things are not always what they seem to be. A persistently positive Papanicolaou smear, after curettage, biopsy, and conization fail to reveal malignancy, certainly causes one to believe the malignant cells are coming, perhaps, from the peritoneal cavity via the Fallopian tube or from the tube itself. Also, the tumor could be situated in a deep cervical gland, which was not included in the cone. Another possibility, not to be overlooked, is a small primary carcinoma of the vagina, mostly submucosa. Such a lesion of the vagina may be multiple and not easily visualized.

It is always interesting to speculate under what circumstances the types of examination mentioned might fail to demonstrate the cancer. I would say that extreme care be utilized first in the vaginal preparation. There should not be any vaginal preparation, as is usually done for vaginal surgery, since the only surface cervical lesion may be completely brushed off by vigorous preparation; second, the cervical canal must be carefully curetted separately, with a small, sharp curette, the cervix being dilated gently, if necessary. Next, a complete but cautious curettage of the uterus should be done, with the material caught on a separate sponge. I am certain more care than usual should be taken in curetting the area near the internal os. This may cause some cervical stenosis, but this is not a difficult situation to correct.

When the conization is performed, I feel it should be done by a sharp knife. Mark off the area of incision well out from the mucocervical junction, and continue backward to just in front of the internal os. To be 100 per cent certain that cancer is not present, it would be required that serial sections be made of this entire cone. The same is true for the scrapings of the cervix and of the uterus.

Also, there is a personal factor which might be in error. There is, at present, too great a variation in the opinions of pathologists and cytologists as to whether the tissue is malignant or whether it is hyperactive epithelium, or hyperplasia. I prefer that whoever reads the original smear should also see the tissue and correlate the two.

We know now, also, from statistics of a large group of cases, that in this Group 4, there is a 3 to 5 per cent error, when a positive test is reported, and this must always be kept in mind when such cases are under investigation.

The best treatment of this patient, at her age of 51, should be a hysterectomy. If she were in her late twenties or early thirties, and in view of the inability to demonstrate cancer by curettage, biopsy, and conization, in an otherwise healthy patient, I would continue to observe her, remembering that 3 to 5 per cent of positive reports are false.

The principal indication for hysterectomy is the continued positive Papanicolaou smear in a patient more than 40 years of age, with the increasing possibility of an intra-abdominal tubal lesion or an untouched deep-seated cervical lesion. The operation indicated is total abdominal hysterectomy because it is so important to inspect for an intra-abdominal lesion and to be able to do glandular dissection, if the specimen at operation shows a deep-seated carcinoma, which has not otherwise been demonstrated.

As it turned out in this patient, a vaginal hysterectomy would have been just as effective, since no carcinoma was found, either in the abdomen or the specimen.

The procedures in this case emphasize not only the value of careful investigation, but that we must, at all times, be absolutely certain that the patient understands the chances of error and these facts be written down on the history. The patient should be in full accord with the medical and surgical decision. Most patients will ask that something be done when they are aware of the facts.

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The findings and clinical history in this patient are exactly those with which the gynecologic clinician is frequently faced. The atypical squamous cells found on the smear of the initial examination are consistent with the clinical diagnosis of cervical polyp. In addition to the obvious clinical finding, the atypical squamous cells also reflect other possibilities such as: local inflammatory disease of the cervix, menopausal vaginitis, Trichomonas, cervical metaplasia, atypical epithelial hyperplasia, atrophy of the vaginal vault consistent with early menopausal changes, carcinoma in situ of the cervix, or even invasive carcinoma of the cervix. On the other hand, the finding of one malignant squamous cell on the smear reflects the strong possibility that cancer is present somewhere, either in the gynecologic tract itself, or in an area such as the peritoneum where it may gain access to the genital structures.

The findings at operation with a pathology report of cervical polyp do not clear the issue so that I would raise the question of the possibility of carcinoma being present within the polyp. This would require multiple blocks and serially stepped sections through these blocks in order to rule out the presence of cancer within the polyp itself. If present, it is quite possible, though not common, for the malignant process to have extended beyond the base of the polyp into the stroma of the cervix. The findings of chronic endocervicitis merely should be considered as false negative biopsy, and should, therefore, call for additional study of the cervix, both that removed by the conization or the removal of additional tissue from the cervix. The secreting endometrium tends to reduce the possibility of menopausal changes.

The cytosmear of March 22, 1957, while strongly suggestive of malignancy, should be called a Class 4 smear and, in the opinion of this consultant, reflects malignancy. Both this smear and the original smear should, therefore, be classified as conditionally positive. The source of this positive smear must be exhaustively explored. At this juncture, I would advise ruling out malignancy in other structures by repeating a complete physical examination, taking roentgenograms of the chest, upper gastrointestinal series, gall bladder series, and barium enema. A cytosmear of an overnight catheterized specimen would also be recommended. The presence of hyperactive cervical squamous epithelium removed at operation on March 22, 1957, means to this observer either atypical epithelial hyperplasia, basal-cell hyperactivity, or dysplasia, which are essentially synonymous and may well be indistinguishable from early cancer or may represent the vanguard of existing carcinoma. The continued finding of atypical squamous cells and cells positive for cancer represents possibilities such as carcinoma of the cervix, of squamous or glandular type, carcinoma of the endometrium with squamous metaplasia

(adenocanthoma—a term not acceptable to this reviewer), metastatic disease, or the reflection of squamous carcinoma primary in the ovary such as might occur in a malignant teratoma.

The onus of responsibility is on the gynecologist to make a diagnosis. In addition to the studies recommended above, I believe that sigmoidoscopy, a flat plate of the abdomen, and an intravenous pyelogram are indicated.

The Schiller test applied to the cervix and vagina may point out areas where biopsy should be concentrated, since even in some instances of carcinoma in situ of the cervix it is possible for the lesion to extend out into the fornices, onto the portio vaginalis, or even to extend down the vaginal tube itself.

If all the above studies are negative, the consultant must, on the basis of three smears interpreted as being positive for malignancy, and two smears containing atypical cells, and cervical squamous epithelium showing atypical changes, remove additional material for the diagnosis. The program recommended by this consultant would be total abdominal hysterectomy with removal of a moderate vaginal cuff. If invasive carcinoma were found within the remaining cervix, I would advise x-ray therapy.

If, at the time of laparotomy, the adnexal structures showed evidence of disease, I would include with the total hysterectomy a bilateral salpingo-oophorectomy. If there were no obvious disease, the adnexa would be conserved. Of course, laparotomy always means exploration of the abdomen.

Editor's Comment

To complete this case it is reported that the management of Patient K. A. S. consisted of a complete abdominal hysterectomy. The normal tubes and ovaries were not removed. Microscopic sections prepared from serial blocks of the cervix revealed a small squamous-cell carcinoma in situ high in the cervical canal.

DIABETES AND PREGNANCY

Mrs. D. K., aged 24 years, a primigravida, is now 24 weeks pregnant. She is 5 feet, 5 inches in height and prior to pregnancy weighed 135 pounds. Her weight now is 154 pounds, a gain of 19 pounds in the first 24 weeks of gestation. She feels perfectly well and has no symptoms. The blood pressure is normal; the pelvis is normal and adequate; the pelvic organs are normal; and the fetal development seems normal. *Sugar* was present in the urine and on two subsequent examinations it persisted.

Problem: 1. The establishment of the diagnosis of diabetes mellitus.
2. The plan of management of this patient if the diagnosis of diabetes mellitus is established.

Consultation

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1. *Establishment of the Diagnosis.*—

Random blood sugar determinations, either fasting or not, may determine the positive diagnosis of diabetes mellitus, but cannot exclude that diagnosis if they are within normal ranges. Any random blood sugar determination of 200 mg. or more of true glucose means diabetes mellitus.

Mrs. D. K. should have a glucose tolerance test. The curve should be back to the normal level in no later than 3 hours, preferably sooner. The peak should not be over 140 mg. true glucose by the Somogyi-Nelson method, or 160 mg. true glucose by the Folin-Wu method. Any pregnant patient is already having a natural cortisone provocative test. I would not use any artificial cortisone provocative test during pregnancy in an attempt to produce a diabetic type curve in a glucose tolerance test. If the glucose tolerance test is normal, I would repeat it monthly for the remainder of the pregnancy and at yearly intervals thereafter. If the glucose test is positive, the patient has either gestational diabetes or diabetes mellitus. The definite diagnosis of diabetes mellitus may not be proved until after parturition. The glucose tolerance test will diagnose the rare case of renal glycosuria.

If the glucose tolerance test is positive, a diabetic type of diet alone may change an abnormal curve to a normal one. If diet alone is insufficient and the curve is markedly abnormal, I would give the patient a screening test with Orinase. This test consists of two blood sugar determinations—the first, one hour before, and the second 3 hours after, a single oral dose of 3 Gm. of tolbutamide.* A drop of 20 per cent or more from the pre-Orinase blood sugar level means that the patient is responsive to the drug and I would start therapy with that drug. If diet and Orinase do not produce normal blood

*Orinase, The Upjohn Co., Kalamazoo, Mich.

sugar and tolerance curves, I would start the patient on insulin. Failure to respond to Orinase, or a later escape from Orinase may become a test to separate gestational diabetes from diabetes mellitus. The Joslin Clinic has not yet been able to carry any patient with diabetes through pregnancy on Orinase alone.

Post partum: Orinase or insulin is gradually reduced and, depending upon blood and urinary sugar determinations, may eventually be discontinued. If glucose tolerance tests become normal, the patient may be given a diagnosis of either gestational diabetes or prediabetes. If the curves continue to be abnormal, and the patient requires the resumption of either Orinase or insulin to produce normal blood sugar determinations she has diabetes mellitus.

Accumulating evidence suggests that all patients who have abnormal glucose tolerance tests should be treated with Orinase or insulin. Infants weigh less and fetal survival rates are higher when mothers with abnormal glucose tolerance test curves receive such treatment during pregnancy.

Management of Mrs. D. K. when not pregnant: Pregnancy is not the only period of stress and strain which may produce an altered glucose tolerance test or reveal diabetes mellitus. Any stress or strain, either physical or mental, may do so. This patient should have daily urinary sugar determinations and, if they are positive, blood sugar determinations, and then glucose tolerance tests whenever she is hospitalized for infections, operations, or trauma, and during periods of great emotional stress.

2. *Plan of Management.—*

Weight control: I would hope and plan to keep this patient's weight at her present level of 154 pounds or 70 kilograms.

Diet: Thirty calories per kilogram of present body weight. The diet would not exceed 2,100 calories and might have to be reduced if the patient continued to gain weight.

Carbohydrate	180-250 Gm.
Protein	2 Gm. per kilogram of body weight
Fat	to complete caloric prescription

This diet should be salt poor to help in preventing weight gain, edema, hydramnios, and toxemia.

Drug therapy: Ammonium chloride (U.S.P.),* acetazoleamide,† and chlorothiazide‡ are adjuncts to the salt-poor diet to help prevent weight gain, edema, hydramnios, and toxemia. Patients who are receiving Diuril should use regular (i.e., salted) bread and butter and should have orange juice at least every other day.

Tolbutamide§ or insulin: If the patient had a satisfactory response to the Orinase screening test, I would start her on that drug. If the response was poor, I would start her on insulin, a mixture of long-lasting and crystalline before breakfast with supplementary doses of crystalline insulin before lunch and dinner and at bedtime according to the urine tests at those times.

Weekly visits to the obstetrician and especially to the internist: This patient needs plenty of instruction and care. She has, at this time, a mild case of diabetes. In the remaining months of pregnancy, this degree of diabetes may progress to the level of total diabetes and the insulin requirement may go up

*Amchlor, Brewer & Co., Inc., Worcester, Mass.
†Diamox, Lederle Laboratories, Pearl River, N. Y.
‡Diuril, Merck Sharp & Dohme, Philadelphia, Pa.
§Orinase, The Upjohn Co., Kalamazoo, Mich.

by leaps and bounds, making it difficult for her to control her rapidly changing disease, even if she had had previous experience and instruction in the management of diabetes. This type of patient is prone to excessive weight gain, edema, hydramnios, and toxemia. For these reasons she should be seen often by the obstetrician.

Hospitalization: The patient should be hospitalized at least one week before the expected delivery date to provide maximum obstetrical and diabetic care for these crucial days and sooner if complications of either diabetes or pregnancy are present.

X-rays: A flat plate of the abdomen should be taken before delivery to rule out any obvious congenital abnormality (hydrocephalus, spina bifida, anencephalus, etc.). Positive x-ray evidence of anomalies might well change the time and type of delivery. Pelvic x-rays should be taken to ascertain the configuration and capacity of the pelvis.

Time of delivery: I believe this patient should be delivered no later than the end of the thirty-seventh week of pregnancy. If serious complications of either pregnancy or diabetes have developed and have not responded to treatment, the patient should be delivered earlier. I dislike delivery prior to the end of the thirty-fifth week of pregnancy unless it is absolutely necessary.

Type of delivery: I would try to perform a pelvic delivery. If there is a vertex presentation and the pelvis is adequate, artificial rupture of the membranes is performed on the predetermined delivery date regardless of the condition of the cervix, but *not* if the vertex is floating. Cautious Pitocin stimulation may be used. If labor develops and proceeds normally, the patient is allowed to continue in labor. If labor has not developed or is not proceeding normally at 6 or 8 hours, then a cesarean section is performed. If the pelvis is borderline and the presentation or position is abnormal, no attempt at pelvic delivery is made. No analgesics or sedative drugs are given for labor. We occasionally employ epidural anesthesia for the last few hours of labor and delivery. Spinal, epidural, caudal, or pudendal anesthesia is used for pelvic delivery; spinal or epidural for cesarean section. Long, hard labors and difficult pelvic deliveries should be avoided. It is very easy to underestimate the weight of these infants and have the shoulders of the infant become impacted. Infants of diabetic patients are very easily traumatized regardless of their size or weight.

Treatment of diabetes during labor and/or operation: We do not change the types of insulin the patient has been receiving or omit it before the delivery day.

Elective cesarean section: The patient receives an intravenous infusion of 10 per cent dextrose in water started preoperatively. One half of the day's dose of insulin is given postoperatively, the other one half with an infusion of 5 per dextrose in water later in the day. The insulin requirement will quickly return to prepregnancy levels. On the operative day, the total insulin dosage is two thirds of that on the last preoperative day and is reduced each succeeding day by about two thirds depending upon blood sugar and urine sugar determinations and insulin reactions. In some patients, the insulin for the first postdelivery day may be reduced to the prepregnancy dose.

Induction of labor: The patient receives the same intravenous fluids. If labor develops and progresses rapidly, the total day's dose of insulin (the same two thirds of the last predelivery day) can be given after delivery. If labor is slow, one half of the day's insulin dose is given after 4 to 6 hours, and the remaining one half after delivery or operation.

Care of the newborn: Infants of diabetic mothers are premature by behavior regardless of weight and size. Aspiration of the nasopharynx and stomach, premature nursery care, oxygen, temperature and humidity control are employed. Precautions for prevention of infection, and, if possible, against the development of atelectasis and hyaline membrane syndrome are taken. Antibiotics are used if respiratory distress or evidence of infection is present. Blood sugar determinations are made on the infants who appear jittery. If the blood sugar is below 30 mg., 5 per cent glucose is given by gastric gavage or intravenously if necessary. Ten per cent of these infants will have a major congenital anomaly. Of these infants with major anomalies, about 50 per cent will not survive. Anomalies may not be obvious at birth, but may manifest themselves hours or days later. Among those to be carefully looked for are congenitally malformed hearts and anomalies of the gastrointestinal tract and genitourinary tract.

Follow-up of infants: A definite percentage of these infants will have either chemical or true clinical diabetes as they mature. Blood and urine sugar determinations should be done annually on all infants of diabetic mothers. Some infants of diabetic fathers will also have congenital anomalies and will become diabetic. They require the same care both immediately and yearly as the infants of diabetic mothers.

Female sex hormone therapy: This is still a controversial point of treatment and the nonusers outnumber the users. I, myself, believe that such therapy is beneficial in minimizing or preventing complications of pregnancy such as premature labor, hydramnios, and toxemia. The Joslin Clinic believes that with female sex hormone therapy the infants of diabetic mothers average a pound less at birth and do not have the typical "Cushingoid" appearance of infants of diabetics. This therapy does not change the percentage of congential anomalies in these infants. Female sex hormone therapy is a supplement to good obstetrical and diabetic care, not a substitute for them.

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1. Establishment of the Diagnosis.—

In order to establish the diagnosis of diabetes mellitus, it is the practice in my clinic to proceed at once to a glucose tolerance test. A postprandial blood glucose level has been used but, although certainly simpler and cheaper, it leaves too many cases in which the diagnosis is uncertain. If the glucose tolerance test is normal, we would then have the uncommon complication of renal glycosuria, which should cause us no concern in pregnancy. As Mrs. D. K. had glycosuria on all three of her examinations, we will expect her to have the typical glucose tolerance curve of diabetes mellitus.

2. Plan of Management.—

For the care of this patient we depend on the assistance of an internist, who will see her at least as often as we do. Later the pediatrician will be called upon to be a necessary part of the team to cope with this difficult complication. A strenuous effort will be made to control at once her diabetes and to maintain her urine in a sugar-free state. If the diabetes can be controlled by diet, this will be done. Otherwise the dose and type of insulin best suited for her needs will be prescribed and changed as needed through pregnancy and the puerperium. During the stressful situations she may encounter,

we will be on the lookout for increased demands for insulin. The most common of the precarious situations we encounter are infections, particularly pyelonephritis, and labor. Increased insulin requirements are recognized and regulated by a more frequent testing of urine for sugar and acetone, supplemented by blood sugar and carbondioxide levels as indicated. Acidosis must be avoided at all cost. If the diabetes becomes difficult to manage at any time, she will be admitted to the hospital.

A chest film is in order despite the notation that "the heart and lungs are normal."

An important objective in Mrs. D. K.'s antepartum care is the prevention of pre-eclampsia. Diabetic patients are more prone to pre-eclampsia and this added complication increases the risk for both mother and fetus. We will hope that scrupulous antepartum care will prevent the superimposition of pre-eclampsia. She will be seen frequently; she will be instructed in self-care for diabetics and in maternity care. We will be certain that she has a diet that precludes any chance of a nutritional deficiency. She will have a hemoglobin or hematocrit test. If anemic, she will be treated with ferous sulfate. As the value of hormone therapy appears extremely doubtful, we will not place her on any schedule of estrogens or progesterone.

A great deal of attention will be paid to weight control, particularly weight increases caused by water retention. As we like to keep a patient within the bounds of 17 to 20 pounds' gain for the entire pregnancy, this patient has already gained too much weight. A strict regimen of salt restriction may produce promptly a loss of the excess water and keep the weight gain within reasonable bounds for the remainder of the pregnancy. A point often overlooked in salt restriction is the avoidance of foods that naturally have a high sodium content. Common offenders in the diets of young housewives are canned soups, luncheon meats, and frankfurters.

If water retention cannot be controlled by salt restriction, a diuretic is needed. For some time we have used acetazolamide,* one tablet a day, with rest periods on weekends, but we are now trying chorothiazide.† The usual dose is 0.5 Gm. a day. It has been effective and safe. We have been on the lookout for potassium depletion but as yet have had no experience with that reported complication.

With all of our diabetic patients we practice preterm delivery. By this I do not mean delivery of a premature infant (5½ pounds or less). When and how to effect this delivery cannot be reduced to any formula and must be prompted by obstetric judgment. The more critical the problem the earlier we are likely to terminate the pregnancy. No patient is allowed simply to go on to term and to enter labor spontaneously. Yet we want to avoid an unnecessarily small baby. The weight of evidence points to the value of eliminating the last 10 to 20 days of pregnancy, a time when the fetus is likely to do better outside the uterus than inside. Clinics practicing preterm delivery appear to have improved their results with diabetic mothers.

If Mrs. D. K. proves to be like one of our typical patients with well-controlled diabetes, she will be admitted to the hospital about the thirty-eighth week of pregnancy, the cervix will be found to be reasonably ripe, and labor will be induced by either rupture of the membranes or Pitocin drip or both.

If she had severe diabetes, if she were a woman with a poor obstetric history or an elderly primipara, or if she had one or more of the more serious complications of diabetes in pregnancy (e.g., nephritis, toxemia, retinitis) we

*Diamox, Lederle Laboratories, Pearl River, N. Y.
†Diuril, Merck Sharp & Dohme, Philadelphia, Pa.

would tend to be more radical in her management. Serious consideration would be given to both cesarean section and delivery before the thirty-seventh to the thirty-eighth week of gestation.

If she develops hydramnios to the point where she becomes extremely uncomfortable, we would aspirate very slowly some of the amniotic fluid through the abdominal wall.

As delivery approaches we will appraise the pelvis carefully to learn whether she can accommodate a large baby. If the baby is undoubtedly a very large baby (9 pounds or over) a section should be considered regardless of the prospects of safe passage through the pelvis.

A pediatrician will have been alerted and, ideally, will be present at delivery. This infant will need the same meticulous attention during the early days of life as does a premature infant. Our babies have not been routinely given increased amounts of carbohydrates because hypoglycemia has not been important.

Editor's Comment

1. The intravenous glucose tolerance curve on Mrs. D. K. was as follows: Fasting blood sugar, 162. Thirty minutes after injection of 23 Gm. of glucose (⅓ Gm. per kilogram) the blood sugar was 210; at the end of one hour, 280; at 2 hours, 200; and at 3 hours, 190. The diagnosis was diabetes mellitus.

There was no clinical evidence of vascular damage. The eye grounds were normal. X-ray of the iliac vessels did not show calcification. She was considered to fall into Class B according to White's standard, with mild diabetes.

2. She was placed on a diet which would favor some weight loss: carbohydrate 200 Gm., protein 90 Gm., and fat 75 Gm., for a total intake of 1,835 calories. She was permitted a free choice of food within this framework to accommodate her appetite. The salt intake was minimal. The total calories were divided into ⅕ at breakfast, ⅕ at lunch, ⅖ at dinner, and ⅕ at bedtime in preparation for the long-acting insulin which was prescribed. She was started on an initial dose of 15 units NPH insulin taken before breakfast. Glycosuria was present postprandially after breakfast and luncheon, with negative urine in the evening and on arising. Therefore a supplemental dose of 6 units of regular insulin was added to her morning NPH. On this dietary regime and insulin dosage, there was a weight loss of 3 pounds in the ensuing month.

At the twenty-eighth week of gestation, carbohydrate, protein, and fat were each increased 10 Gm. to stop further weight loss and NPH insulin was increased to 18 units. On this management, she spilled 8 Gm. of sugar in 24 hours. This amount was considered desirable in order to avoid hypoglycosuria following her night feeding and during the night.

At the thirthieth week of pregnancy a change in her diabetic status was noted with increasing glycosuria. At this time, it was found necessary to increase the morning dose of NPH insulin by 6 units and crystalline insulin by 4 units. The totals now were NPH 24, regular insulin 12.

In the thirty-sixth week of gestation, the baby's weight was estimated to be about 3,500 grams. The cervix at this time was long and closed. The presenting part was dipping into the pelvis but was not engaged. It was decided that the most expedient method of terminating the pregnancy would be by cesarean section. This was duly carried out after the following preparation:

Five days before the expected delivery, the patient was hospitalized, and taken off of long-acting insulin. Multiple doses of regular insulin were given

before each of the prescribed meals. Her insulin requirements were 16 units of regular insulin before breakfast, 10 units of regular insulin before lunch, and 10 units before supper.

On the day of operation (the end of the thirty-sixth week) 5 per cent glucose with 0.45 per cent saline (half strength) was started intravenously. Atropine was given 30 minutes before operation. After complete preparation with the patient draped and the surgical team scrubbed and gowned, general anesthesia was induced with intravenous Pentothal sodium followed by ethyline and oxygen. The baby was delivered within 3 minutes of actual induction and cried lustily. He weighed 3,720 grams. After the birth of the baby, Mrs. D. K. was given 100 mg. Demerol intravenously.

The air passages of the baby were cleared with a tracheal catheter and he was placed in a heated bassinet. The stomach was not aspirated. The baby was placed in an incubator and was stimulated during the first 4 hours. Nothing was given by mouth during this period. Mother's milk was begun the second day—1 ounce every 2 hours. By the third day the baby was receiving routine care.

Postoperatively, Mrs. D. K. received a total of 300 c.c. of intravenous glucose and saline. This provided 150 Gm. carbohydrate, and 13 Gm. sodium chloride. It was covered by 30 units of regular insulin, 10 units per flask.

On the second day, the patient was able to take food in the form of fluids and was given regular insulin in divided doses of 8, 8, and 8 units. On the third day, long-acting insulin was again administered, 18 units NPH, with a supplemental dose of 10 units of regular insulin before the evening meal. The patient was discharged on the tenth day and maintained on a dietary regime of 225 Gm. carbohydrate, 80 Gm. of protein, 80 Gm. of fat, and 18 units of NPH insulin.

Reviews and Abstracts

EDITED BY LOUIS M. HELLMAN, M.D.

REVIEWS OF NEW BOOKS

Pediatric Gynecology. By Goodrich C. Schauffler. Fourth edition, 349 pages with 84 illustrations. Chicago, 1958, The Year Book Publishers, Inc. $9.00.

To contemplate a new edition of a recognized gynecologic work must present certain challenges to the author. A completely new revision must tax one's capabilities to the utmost.

In this, the fourth edition of *Pediatric Gynecology,* the author has included a new chapter on intersexes and female pseudohermaphroditism, and expanded the chapters on vaginal conditions and menstrual disorders.

The chapter on special methods of investigation remains required reading for all those who are confronted with the often perplexing task of doing a thorough gynecologic examination on infants and children. Chapters on general surgical, special urologic and proctologic considerations add much to the merit of this book.

The author is not content with presenting the purely medical approach to his subject but includes chapters on social service, medicolegal aspects, and weaves an acute awareness of psychosomatic problems into the over-all picture.

Thus one welcomes to the desk a successful task admirably done.

Psychoprophylactic Preparation for Painless Childbirth. By Isidore Bonstein. 143 pages with 14 figures. New York, 1958, Grune & Stratton. $2.50.

Reviewing a book like *Psychoprophylactic Preparation for Painless Childbirth* presents certain problems for a practicing obstetrician. In the first place it is either a translation or has been written by a Frenchman who speaks English. The phraseology is at times unique if not naïve. In the copy of the book I received, Dr. Bonstein is not identified in any way. He obviously is not an obstetrician, so I must assume that he is a psychiatrist.

Both Dr. Bonstein in the text and Dr. Lamaze in the preface say that the psychoprophylactic method is entirely different from natural childbirth (childbirth without fear) or from hypnotism, but I am not sure. I have all the respect in the world for I. P. Pavlov and I know that when he rang a bell his dogs salivated. To assume, however, that a pregnant woman in seven short months, or eight easy lessons, can eliminate "century old" conditioned reflexes and establish a brand-new group that say when the bell rings there is no pain, is to me unbelievable. I have been very interested in natural childbirth or, as we call it, "Preparation for Labor," but even in the most relaxed and understanding patient I have always been told by her that it hurts, but not too much. It seems to me that Dr. Bonstein, Dr. Lamaze, and their school give a more palatable explanation for

what to me is still a form of self-hypnotism and explicit faith in one's obstetrician and those who help him, plus a certain amount of relaxation and common sense on the part of the patient.

Time will not permit me to elaborate on all of the bizarre concepts in this book. I must, however, speak of those that are to me bad obstetrics or unworkable in the world in which we live. Page 35, Chapter 5, makes the blanket statement, "If she follows the teaching and *behaves correctly* she will experience *no pain* and *no discomfort.*" In the next paragraph it says: "If disturbances of some consequences are noticed in this field, they should be corrected by suitable psychotherapy." Is life so simple for either quotation?

The next paragraph: "Clinical determination of the nervous type is advisable." All my patients are nervous at first. "Best results are obtained with women of strong and well-balanced character." This latter group need no preparation; I worry about the nervous type.

The next few chapters are designed to send chills down the spine of the Hospital Accreditation Board and the Department of Health of any city. It is wrong to quote out of context, but for the sake of brevity I must: "The ideal type of building has the appearance of a good hotel." This refers to the maternity hospital. "Flowers, pastel colors, indirect light. . . ." "At the very beginning of her labor, the parturient may stay in the 'Entertainment Lobby' (or 'chit-chat lobby')." This goes on till the cervix is more than 5 cm. dilated. "The name 'progress room' is more suitable than 'labor room.' It is often advisable to put a woman in labor with a *recently delivered mother.*" This is repeated several times. "If the patient is accompanied by a person who seems unsuitable or because of poor education uses inappropriate language, such as she 'has pains,' that person should be eliminated." No enemas are given; no rectal examinations are done, both might cause pain. Only gentle vaginal examinations should be done ("sometimes these hurt"). These patients may have frequent sips of water. This is up to and beyond 5 cm. dilatation. How does anyone know that an emergency may not arise necessitating an anesthetic?

Then come eight lectures, the same eight we read before—only more elaborate. I forgot to mention that leg stirrups are not used. Parturients must not be left without fluid and some very light food during the earlier course of labor (again up to 5 cm., because the patient is not examined until she goes to the progress room). Apparently no one ever gets a tear.

I am not making fun of the book. I think it has been carefully thought out and well written, and I am sure that the results are as stated. However, in this country in our hospitals as they are now organized, to carry out such a program would not only be impossible—but I feel definitely that much of the routine as outlined is not good obstetrics.

The Healing of Wounds—A Symposium on Recent Trends and Studies. By Martin B. Williamson. 202 pages. New York, 1957, McGraw-Hill Book Company. $7.00.

Basic processes involved in the healing of wounds are given a rather complete summary in view of current knowledge. Such topics as the metabolism of proteins and amino acids during wound healing, the role of the ground substance in wound healing, methionine during protein starvation, pharmacologic considerations of sulfur compounds in tissue regeneration, and vitamin C in its relation to wound healing are discussed in detail by different contributors. Of special interest to the gynecologic clinician is the chapter by Herbert E. Schmitz on incisions used in gynecology. This chapter presents an interesting survey of some of the factors which contribute to the failure of healing of incisions on the basis of an extensive study of over 10,000 laparotomies. Another eminently practical and beautifully written chapter is that by Harold B. Haley on clinical approaches to the various concepts of wound healing. In this section, the author discusses the wound in its environment, and local care of the wound.

It is the authors' contention that both the biologic and molecular approaches to the study of this problem are necessary, and the preliminary chapters summarize many of the biochemical studies on wound healing undertaken since the last war. The information contained in the book will be of interest to all surgeons, and not the least useful feature of the volume is the excellent bibliography which follows each chapter. Although the book is nicely printed and bound, the price of $7.00 seems somewhat excessive.

Endocrine Aspects of Breast Cancer. By Alastair R. Currie. 340 pages with 108 figures and 99 tables. Baltimore, 1958, The Williams & Wilkins Company. $8.50.

This monograph reports the proceedings of a conference on Endocrine Aspects of Breast Cancer held in Glasgow, Scotland, in July, 1957. Participants included physicians, surgeons, endocrinologists, and biochemists interested in breast carcinoma from Great Britain, Sweden, Holland, Germany, Italy, the United States, and New Zealand.

The monograph is divided into four parts: clinical, pathology, hormone studies and experimental pathology. The clinical section discusses the effects of ablative procedures in the management of carcinoma of the breast including adrenalectomy and gonadectomy and hypophysectomy, both surgical and isotopic. This section is well presented and emphasizes many of the difficulties involved in evaluating the clinical effectiveness of these procedures.

The section on pathology deals with the pharyngeal hypophysis, histological and chemical studies of the adrenal glands in patients with breast carcinoma, and with the human anterior hypophysis in patients with breast carcinoma, as well as pathological changes in the human breast.

The section on hormone studies is an excellent section of our present state of knowledge of the anterior pituitary hormones and mammotrophins, urinary estrogens, urinary gonadotrophins, and urinary oxysteroids. The papers presented are critical and lead to the conclusion that, while extensive investigations are being pursued, the biochemical data which has accumulated to date gives no inkling as to the mechanisms involved in hormone-dependent breast cancer. There is no useful index at present to predict the breast cancer patient who will respond favorably to endocrine ablative surgery nor to distinguish this patient from one in whom the disease progresses following ablative therapy.

The final section on experimental pathology reviews the endocrine aspects of mammary growth and function particularly in relation to the pituitary hormones as well as hormonal mechanisms in mammary carcinogenesis.

These are excellent review articles. This monograph will be extremely useful to all physicians and biochemists interested in the problem of breast carcinoma and particularly in the role of hormone influences in this disease.

Atlas der Kolpomikroskopie. By Tassilo Antoine and Viktor Grunberger. 244 pages with 176 illustrations. Stuttgart, 1956, Georg Thieme Verlag.

A most carefully prepared and illustrated compendium of the colposcopic picture in various lesions of the uterine cervix with their histologic equivalent is presented by Drs. Antoine and Grunberger. After a brief history of colpomicroscopy and a careful description of the technique of the examination, the authors present a thoroughly illustrated description of the instrument itself and a brief summary of clinical colposcopic methods. The remainder of the book is an atlas in which normal and abnormal cervices are illustrated by means of colposcopic photomicrographs with corresponding histologic slides on the same page. Typical sections of leukoplakia, papillomas, erosions, carcinoma of the cervix and vulva, and various endometrial and ovarian lesions are illustrated. Although incident-light microscopy of cut sections of removed tissues would appear to have limited practical value, the authors suggest that this method might be substituted for frozen-section techniques in certain selected cases. Its value in clinical examination of the epithelium of the vagina is considerably greater, and the correlations between the colpomicroscopic views and the histologic preparations are convincingly suggestive of the helpfulness of the method.

The book is beautifully printed and bound, and the illustrations, although almost entirely in black and white, are clear and well reproduced. The legends of each illustration are printed in German, English, and Spanish, and there is a brief English summary of the preliminary section on the technique of examination.

BOOKS RECEIVED FOR REVIEW

Anaesthesia for Nurses. By Eric Godwin. 98 pages, 12 figures. Baltimore, 1957, Williams & Wilkins Company. $2.50.

Chemistry and Biology of Mucopoly-Saccharides—Ciba Foundation Symposium. By G. E. W. Wolstenholme and Maeve O'Connor. 323 pages, 48 illustrations. Boston, 1958, Little, Brown & Co. $8.50.

Cholesterol as Related to Atherosclerosis—A Review of the Literature 1950 to July, 1957. By Helen I. Mattill. 67 pages, 5 figures. Chicago, 1957, Cereal Institute, Inc.

Essentials of Gynecology. By E. Stewart Taylor. 502 pages, 343 figures, 4 plates, 7 tables. Philadelphia, 1958, Lea & Febiger. $12.00.

Fator vascular do endometrio na etiopatogenia das hemorragias disfuncionais. By Carlos Alberto Salvatore. 237 pages, 35 figures, 2 tables, 2 plates. São Paulo, 1955, Empresa Grafica Editora Guia Fiscal, Jose Ortiz Junior.

Oestrioluitscheiding in de Urine en de Anatomische Toestand van de Placenta (Speciaal Bij Toxaemie). By G. J. W. H. Lenters. Groningen, 1958, J. B. Wolters.

Psychoendocrinology. By Max Reiss (with 23 contributors). 208 pages, 36 figures, 22 tables. New York, 1958, Grune & Stratton. $7.00.

Tumori della vescica nei lavoratori delle amine aromatiche. By Ettore Mattea. 103 pages, 13 tables. Milano, 1958, Casa Editrice Ambrosiana.

SELECTED ABSTRACTS

Acta obstetricia et gynecologica scandinavica

Vol. 37. Supp. I, April, 1958.

Arén, Per: On Legal Abortion in Sweden: Tentative Evaluation of Justification of Frequency During Last Decade, pp. 1-75.

Since the expansion of the Swedish Abortion Law in 1946 gynecologists are not infrequently requested to induce abortion on medicosocial grounds. During the last decade the frequency of legal abortions has been fairly high, and in 1951 it reached a maximum of 57.4 per 1,000 living children born. The increase in frequency of legal abortion in Sweden has been disquieting, especially as no evidence has been produced that criminal abortion has become less common. Much suggests that the total number of abortions has not decreased, but increased. It has been suggested that since 1946 a new type of abortion clientele has developed, one consisting mainly of married women. Furthermore, the Abortion Law presupposes prognostication for which no methods are as yet available. The law legalized the induction of abortion if, in view of the living conditions and other circumstances, it may be assumed that the mother's physical or mental strength would be sincerely impaired by the arrival and care of the child. This new indication was called "foreseen weakness," and placed a heavy burden on the shoulders of psychiatrists and gynecologists.

In an attempt to assess the justification for the frequency of legal abortion during the last decade in Sweden, the author made an analysis of data obtained from the hospital records

of 248 women who had had legal abortions induced and had become pregnant (389 pregnancies) again. About one fourth underwent a new legal abortion (one third had applied) while about two thirds gave birth on one occasion or more (remainder: extrauterine pregnancy, spontaneous or criminal abortion).

Interviews of 100 unselected women who had had a legal abortion prior to giving birth to a child revealed that none of the latter pregnancies had been accompanied or followed by any appreciable injury to their health or impairment of their working capacity. About one half of these 100 women were living under similar conditions as at the time of legal abortion. Fourteen women stated that they had desired to have a substitute for the child they had earlier not borne, and 20 stated that, although the pregnancy was unwelcome, they could not bear the idea of going through a new abortion.

Of 197 women in whom pregnancy had not been interrupted although legal abortion had been granted, 2 had died and 33 had had miscarriages. The remaining 162 women gave birth. The child died during or within one week of delivery in 7 cases (5 per cent). In 12 cases (7 per cent) the women had the child adopted. The remaining 143 (88 per cent) kept the child. The abortion had been granted in all these cases on psychiatric or sociopsychiatric grounds. In none of the cases did any serious complication occur during pregnancy or delivery. In 94 per cent the women were psychologically adjusted to the child. In 79 per cent of cases mental health was as before or better. In the remainder (21 per cent) mental health had become worse but the deterioration was usually insignificant, and in approximately half of the cases it was apparently due mainly to factors other than the arrival of the child. The subsequent course showed that it was justified to refrain from operation in 127 cases (89 per cent) but not in the remaining 15 (11 per cent). One woman who had schizophrenia both at the time of application and of the review could not be satisfactorily interviewed and was excluded in the analysis.

The author concluded that if legal abortion is to be regarded as a therapeutic measure, the observations set forth above suggest that a more restrictive attitude should be adopted in the evaluation of the grounds for legal abortion.

ROBERT E. L. NESBITT, JR.

British Medical Journal

Vol. 1, April 5, 1958.

Burnard, E. D.: A Murmur From the Ductus Arteriosus in the Newborn Baby, p. 806.

In a study of 100 babies examined at birth, 37 were noted to have a rough murmur which was heard in late systole. The murmur resembled that of a persisting ductus arteriosus as exemplified by its quality on auscultation, manner of induction on the chest wall, and phenocardiographic properties. It was felt that in babies who were mildly asphyxiated, contraction of the ductus occurred as in asphyxiated lambs, causing the majority of the murmurs.

ROBERT C. KNAPP

Irish Journal of Medical Science

No. 386, February, 1958.

Bancroft-Livingston, G., and Myles, T. J. M.: Uterine Rupture in Late Pregnancy and Labor, p. 81.

Sixty-seven cases of rupture of the uterus during a period of 11 years are reported. The distribution of the cases with respect to parity shows that the rupture occurred in 41 of the 67 cases in the fifth or subsequent pregnancy. In 8 of these cases the rupture occurred during pregnancy and all in uteri containing scars. Cesarean section scars were responsible in 7 instances, 6 of which were of the classical type.

Spontaneous rupture during labor of the unscarred uterus occurred in 19 cases, 14 of these in women during their fifth or subsequent pregnancy. In most of the cases no predisposing factor could be found. Malpresentations of the fetus have often been blamed

but in this series the presentation was vertex in 15 cases, breech in 2 cases, shoulder in one case, and unknown in one case. Four ruptures occurred with the injudicious use of oxytocic drugs.

Rupture of a previous cesarean section scar during labor accounted for 9 cases, 3 of which were in previous classical and 6 in lower segment scars.

Traumatic rupture during labor was the chief cause in the series, accounting for 25 cases. Internal version was responsible for 11 cases and attempts at forceps delivery for 6. The remaining 7 cases included conditions such as manual removal of the placenta and previous cervical amputation. There was only one case of a ruptured myomectomy scar.

The treatment employed was hysterectomy in 47 cases. In a number of the cases the hysterectomy was subtotal, sometimes as a time-saving procedure and sometimes the method of choice because of the tear lying transversely in the lower segment. In 7 cases repair of the rupture was carried out. It is noted that this treatment must sometimes be considered.

The maternal mortality in the entire series was 19.4 per cent and the uncorrected fetal mortality 83.6 per cent.

EDWARD SOLOMONS

Holland, P. D. J.: The Investigations of a Ward Outbreak of Staphylococcus Pyogenes Infection, p. 92.

In an outbreak of *Staphylococcus pyogenes* infection affecting a geriatric ward, 6 of 15 patients and 1 of 4 nurses developed severe skin lesions. The nasal carrier rate at the outset was 90 per cent and fell to 37 per cent when the infection was brought under control largely by the use of nitrofurazone solution. Antibiotic-resistant strains could not be isolated from the skin lesions, but this does not reduce the importance of the nasal resistant strains as potential pathogens.

The contribution of the nursing staff to the dissemination of the organism was very considerable and emphasis was placed on the paramount importance of general ward hygiene which has in this antibiotic era been somewhat neglected.

EDWARD SOLOMONS

No. 387, March, 1958.

Hackett, W. E. R., and Dawson, G. W. P.: The Distribution of the ABO and Simple Rhesus (D) Blood Groups in the Republic of Ireland From a Sample of 1 in 37 of the Adult Population, p. 99.

Studies were made on 55,696 Irish ABO and simple Rh groupings. They were arranged according to the counties of birth of the donors of the blood. The most striking feature of the ABO group pattern is the high incidence of group A in those areas of the Republic of Ireland which received the bulk of Anglo-Norman and later English population settlement since the twelfth century A.D. There is more Rh negativity in the east of Ireland than in the west and the reason for this is not quite clear, being possibly related to the population history of the country prior to the twelfth century A.D.

EDWARD SOLOMONS

Journal of Clinical Endocrinology and Metabolism

Vol. 17, 1957.

McBride, J. M.: Estrogen Excretion Levels in the Normal Postmenopausal Woman, p. 1440.

The cessation of menstruation at the time of the menopause is not invariably accompanied by atrophic changes in the genital tract. It is possible that there is continued action of estrogens in the normal postmenopausal woman.

The author determined the 24-hour urinary output of estrogens twice a week for 6 to 8 weeks of 7 normal elderly postmenopausal women.

The same determinations were made on the urine of 38 patients who had simple atrophy of the endometrium and of 8 patients who had cystic atrophy of the endometrium. In addition, 4 patients with cystic glandular hyperplasia were studied.

The following conclusions were arrived at after the above study:

1. The quantity of estradiol, estrone, and estriol in the urine of the normal postmenopausal woman is comparable to the amount excreted by women in the resting phase of the menstrual cycle.

2. There are no cyclic variations in the excretion of estrogen metabolites.

3. The quantity of estrogen excreted bears no direct relationship to the histologic pattern of the endometrium.

4. The postmenopausal woman produces comparable amounts of estrogen even after bilateral oophorectomy.

J. EDWARD HALL

Journal of Clinical Investigation

Vol. 37, 1958.

Brown, A. K., and Zuelzer, W. W.: Studies on the Neonatal Development of the Glucuronide Conjugating System, p. 332.

Liver enzyme systems are involved in the conjugation of glucuronic acid with numerous endogenous and exogenous substances. This is one of the major detoxification mechanisms of the body. Among endogenous substances conjugated in this manner are steroid hormones and "indirect" bilirubin.

Jaundice of newborn infants is attributable to indirect (unconjugated) bilirubin and this fact suggested the present study. Livers were obtained from fetal newborn and adult guinea pigs, homogenized, and differentially centrifuged. Glucuronyl transferase was obtained from the microsome fraction and uridine-diphosphate-glucuronic acid (UDPGA) dehydrogenase was partially purified from the supernatant solution.

In mid-pregnancy the fetal liver had almost no glucuronide-conjugating activity; at birth the activity was about one-fifth that of the adult and by about the twentieth day the enzyme system was nearly "matured." Both glucuronyl transferase and UDPGA dehydrogenase were markedly deficient in the fetal liver. After birth, their rise was approximately parallel and almost linear with time. (Similar findings in rats have been reported very recently by Grodsky, Carbone, and Fanska: Proc. Soc. Exper. Biol. & Med. 97: 291, 1958, and by Lathe and Walker: Biochem. J. 67: 9P, 1957, who studied homogenates of human fetal livers.)

LEON C. CHESLEY

Journal of Obstetrics and Gynaecology of India

Vol. 7, 1957.

Bose, Sudhir: Cardiac Diseases Complicating Pregnancy. A Clinical Review of 102 Cases, p. 237.

Heart disease with pregnancy presents a peculiar problem in Bengal because most maternity centers cater to women from the lowest income group and from destitute and uprooted refugee families who are admitted either with cardiac failure or with labor well advanced.

The study of 102 cases of heart disease admitted at Eden Hospital in 1955 represented an incidence of 0.45 per cent of the total number of confinements. Complete biochemical tests were carried out to exclude any complicating disease (toxemia and nephritis).

Rheumatic heart disease, though commonest in the series, comprised only 64.7 per cent of the cases—a much lower figure than those cited in other countries. On the other hand, hypertensive heart disease was more frequent.

In the rheumatic group, involvement of the mitral valve was met in 56 cases, and 10 cases were combined mitral and aortic. The low incidence of the latter may be attributed to the neglect of treatment and death at an earlier age. Anemia with hemoglobin between 4 to 7.5 Gm. was present in 35 per cent of the patients.

It was noted that heart failure developed about the age of 25 years. This was explained by early marriage and frequent pregnancies precipitating decompensation at a younger age. Patients with 3 or more children are more likely to belong to Functional Group III or IV; but in this series there were 25 primigravidas and 3 of them died. Most patients sought medical aid when they reached Stages III and IV.

The obstetrical management was always directed toward a safe vaginal delivery without producing any exhaustion in the mother. In none of the cases was there any trial or induction of labor. The majority of deliveries were spontaneous or by low forceps. All patient were kept in an observation ward for 24 to 48 hours after delivery. Pituitary and ergot preparations were avoided.

The maternal mortality was 7.8 per cent and the maternal morbidity was 10.8 per cent. The fetal mortality was 12.7 per cent. The maternal and fetal mortality was unusually high because of the large number of emergency admissions of patients with gross cardiac lesions.

JOHN J. DETTLING

Masani, K. M.: A Review of Forty-Seven Cases of Cardiac Disease During Pregnancy, p. 242.

A review of 47 cases of cardiac disease is presented by the author. The incidence of cardiac disease in this series was 0.2 per cent of the total number of confinements. The authors stated that 89.4 per cent of the cases were of rheumatic origin, with mitral stenosis alone accounting for 61.7 per cent. A comparison of the incidence of rheumatic heart disease in other countries showed little difference in the incidence of cardiac disease of rheumatic origin in tropical and in temperate climates.

With increasing age and parity the incidence of severe decompensation increases. Cases of severe decompensation were met with, however, in multiparas below the age of 20. The probable reasons for such early manifestations of cardiac failure are anemia, economic conditions, and repeated pregnancies. There were 18 cases of Class I, 21 of Class II, 4 of Class III, and 4 of Class IV.

Patients in Class I had no symptoms and were diagnosed during routine antenatal care. In patients in Class II, dyspnea on exertion was the chief symptom, while many had persistent cough and edema as well. Patients in Classes III and IV had dyspnea, orthopnea, cough, and edema.

Three patients died. One died undelivered from pulmonary edema; one died from congestive heart failure 8 hours after delivery; one died from pulmonary embolism 5 days after delivery.

JOHN J. DETTLING

Items

American Board of Obstetrics and Gynecology, Inc.

The American Board of Obstetrics and Gynecology is pleased to announce the certification of the following doctors at the Part II Examinations held in Chicago, Illinois, May 9 through 16, 1958.

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Mendelowitz, Stanley M.	15 Ellis Place	Ossining, N. Y.
Mercer, Jack P.	1948 Broadway	Lorain, Ohio
Merryman, William B.	9 Buttles Ave.	Columbus 8, Ohio
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Monson, E. Conrad	2955 Harrison Blvd.	Ogden, Utah
Montz, Charles R.	221 5th St.	Bismarck, N. D.
Moore, Jack	426 Hermann Professional Bldg.	Houston 25, Texas
Moore, Richard M.	3200 University Ave.	Des Moines 11, Iowa
Morese, Kenneth N.	6407 USAF Hospital, APO 323	San Francisco, Calif.
Morley, George W.	Women's Hospital	Ann Arbor, Mich.
Morrison, Richard C.	111 St. Matthews Ave.	San Mateo, Calif.
Murphy, William H.	15 Clinton Ave.	Rockville Centre 2, N. Y.
Murrieta, Thomas	9210 S. Colima Road	Whittier, Calif.
Nickens, Oswald J.	2035 Centre Ave.	Pittsburgh 19, Pa.
Niswander, Kenneth R.	412 Linwood Ave.	Buffalo 9, N. Y.
O'Connell, Franklin T., Jr.	1737 W. Howard	Chicago 26, Ill.
Olson, Albert W.	1700 Brooklyn Ave.	Los Angeles 33, Calif.
O'Neill, Edward	Roosevelt Clinic	Hato Rey, P. R.
Orcutt, Roberts E.	University of California Hospital	San Francisco, Calif.
Overbeek, Ernest L.	512 Medical Arts Bldg.	Grand Rapids, Mich.
Paul, Gerson S.	1323 W. Tabor Road	Philadelphia 41, Pa.
Pauly, James P.	212 S. 11th St.	La Crosse, Wis.
Payne, Francis R., Jr.	722 S. Adams St.	Petersburg, Va.
Pearce, Eugene W. J.	5920 Nall Ave.	Mission, Kan.
Peerman, Charles G., Jr.	1211 21st Ave., S.	Nashville, Tenn.
Peterson, William F.	1100th USAF Hospital	Bolling AFB, D. C.
Porter, Bruce M.	2232 N. 7th	Grand Junction, Colo.
Porter, Frederick G.	27459 W. Seven Mile Road	Livonia, Mich.
Porter, James O., Jr.	502 Donaghery Bldg.	Little Rock, Ark.
Posner, Norman S.	1100 Grand Concourse	Bronx 56, N. Y.
Price, Thomas P., Jr.	400 Park Ave.	Yankton, S. D.
Prince, Addison E.	8942 Dexter Blvd.	Detroit 6, Mich.
Quinlan, Richard S.	102 Park Ave.	Yonkers 2, N. Y. (Single certification in *Obstetrics*)
Rapoport, Leonard P.	55 East Washington	Chicago 2, Ill.
Reynolds, A. Gordon	233 Cajon	Redlands, Calif.
Rights, Clyde S.	4747 Mission Blvd.	San Diego 9, Calif.
Riordan, Gerald T.	701 S. Second	Springfield, Ill.
Ritter, Hubert A.	16 Hampton Village Plaza	St. Louis 9, Mo.
Roberts, Harry L., Jr.	2113 Fifth Ave.	San Diego 1, Calif.
Roberts, Lucien W., Jr.	1523 Wilborn Ave.	South Boston, Va.
Rogers, Wayne S.	220 Miracle Mile	Coral Gables, Fla.
Rose, David J.	Medical Arts Bldg.	Princeton, N. J.
Rosen, Marvin I.	1323 W. Tabor Road	Philadelphia 41, Pa.
Rotchford, John G.	Medical Center Bldg.	Spokane 4, Wash.
Roy, William R.	202 Medical Arts Bldg.	Topeka, Kansas
Rugh, Walter B.	6833 Wooster Pike, Mariemont	Cincinnati, Ohio
Ryan, Ralph G.	105 South York	Elmhurst, Ill.
Sacks, Seymour	101 Garden St.	Needham, Mass.
Sands, Joseph S.	40 Pleasant St.	South Weymouth 90, Mass.
Saunders, John R.	Suite 14, Medical Center	Lynchburg, Va.
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Schoeneck, Henry W.	1028 State Tower Bldg.	Syracuse, N. Y.
Schrepfer, Rosemary	39th & Rainbow	Kansas City, Kan.
Schroll, Jack C.	211 Wolcott Bldg.	Hutchinson, Kan.
Seear, Torben	114 W. Third Ave.	Gastonia, N. C.
Siever, James M.	641 New Moore Bldg.	San Antonio 5, Texas
Simonson, Emmett D.	10515 Carnegie Ave.	Cleveland 6, Ohio

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Smart, Leon A.	4069 Easton Ave.	St. Louis 13, Mo.
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Stavig, Paul H.	4161 USAF Hospital	Davis Monthan AFB, Ariz.
Stella, Frank	159 Main St.	Malden, Mass.
Stewart, Robert C.	802 North 6th St.	Birmingham 4, Ala.
Stoudemayer, Tullious C.	15 Medical Court	Greenville, S. C.
Sullivan, Cornelius J. P.	1 Post St.	Yonkers, N. Y.
Sullivan, John J.	606 North Brand	Glendale 3, Calif.
Summerlin, Arthur R.	2115 Clark Ave.	Raleigh, N. C.
Summerson, Donald J.	US Army Hospital	Fort Dix, N. J.
Swan, James E.	1828 S. Western Ave.	Los Angeles 6, Calif.
Swann, Raymond O.	University Hospitals	Iowa City, Iowa
Sweeney, William J., III	530 E. 70th St.	New York 21, N. Y.
Taylor, George J., III	US Naval Hospital	Memphis, Tenn.
Tischler, Stanley H.	60 Plaza St.	Brooklyn 38, N. Y.
Tomsu, Glenn F.	310 E. Water St.	Port Huron, Mich.
Trisler, John D.	3001 W. Grand Blvd.	Detroit 2, Mich.
Tucker, Wilson D.	US Naval Hospital	Newport, R. I.
Turman, Prentiss A.	1435 Madison	Memphis, Tenn.
Turnbull, Frank T.	2 West Fern Ave.	Redlands, Calif.
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Ulmer, Arthur A.	14616 E. Seven Mile	Detroit 24, Mich.
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Vermeeren, Jacques A.	Beckley Mem'l Hosp.	Beckley, W. Va.
Wachsman, Max	30 E. 60th St.	New York 22, N. Y.
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Young, Alma L.	3343 W. Penn St.	Philadelphia, Pa.
Zerzavy, Frederick M.	University Hospitals	Baltimore 1, Md.

Canadian Society for the Study of Fertility

The Canadian Society for the Study of Fertility will hold its annual meeting in London, Ontario, Canada, on Oct. 31 and Nov. 1, 1958. Communications in regard to it can be addressed to Dr. Jean F. Campbell, Secretary-Treasurer, 238 Queen's Avenue, London, Ontario, Canada.